Bone metastases of prostate cancer: Molecular mechanisms, targeted diagnosis and targeted therapy (Review)

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Abstract. Prostate cancer (PCa) is second only to lung cancer in terms of death among men worldwide. Advanced PCa frequently results in bone metastases, which occur in ~90% of patients and frequently result in severe skeleton-related events. Currently, the treatment for this disease is limited to alleviating its clinical symptoms and cannot provide a complete cure. Therefore, the development of novel treatment strategies is particularly important. In recent years, numerous novel strategies for the diagnosis and treatment of PCa have emerged, resulting in good clinical efficacy. For example, strategies targeting prostate specific membrane antigen, poly ADP-ribose polymerase and programmed cell death protein 1 have been applied to PCa-induced bone metastasis, and have shown initial efficacy and great potential. Therefore, understanding the molecular mechanisms underlying the formation of bone metastases in patients with PCa is of importance for the effective management of this disease. The purpose of the present review is to comprehensively outline the roles of protein-coding genes and non-coding RNAs in the development of bone metastases of PCa to elucidate their significance in the management of PCa. The aim is to offer clinicians and researchers a comprehensive understanding of this topic.

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1. Introduction

Among all malignancies, prostate cancer (PCa) is the primary cancer in men and the second highest contributor to mortality (1,2). Metastatic PCa, which is often deemed incurable, has a 5-year survival rate of only 25% in contrast to the 99% survival rate of localized PCa (3,4). Studies have indicated that 80-90% of individuals diagnosed with advanced PCa will ultimately experience the development of bone metastases (5-8). Advanced PCa is usually treated with drugs or surgical castration (9,10). Most castration-resistant PCa (CRPC) is ultimately incurable, and CRPC is often accompanied by the risk of bone metastasis (11,12). Patients with bone metastases are prone to skeleton-related events, including unbearable bone pain, which reduces the quality of life of patients and increases the chance of death (13,14). The axial bone is the most common site of PCa metastases, especially in the pelvis or spine (15).

The identification and management of bone metastases in patients with PCa pose difficulties. In the past few years, the introduction of positron emission tomography/computed tomography (PET/CT) has transformed the way patients with PCa-induced bone metastasis are diagnosed and treated. Scientists created PET/CT-targeted prostate specific membrane antigen (PSMA) (16), which can be used for molecular imaging-based diagnosis. This technique has been widely used in the diagnosis of PCa-related bone metastases (17-20). Furthermore, conducting a bone tissue biopsy has remained the most precise technique for detecting bone metastases at present. However, the limited clinical application of these methods is attributed to invasive surgical procedures, a lack of specificity, high expenses and the potential hazards of radiation exposure (21). Therefore, in-depth exploration of the molecular mechanisms of PCa-induced bone metastasis is needed to identify valuable diagnostic and therapeutic biomarkers.

The high tendency of bone metastasis of PCa is related to numerous factors, and the complete molecular process that underlies the formation of bone metastases remains unclear. A study has indicated that the factors influencing the tendency of PCa to metastasize to bones mainly include the tumor microenvironment, interactions between cancer cells and bone matrix cells, the expression of specific proteins such as bone morphogenetic protein (BMP) and receptor activator of NF-κB ligand (RANKL), and the activation of signaling pathways that promote the activities of osteoblasts

and osteoclasts (22). Previous studies have confirmed that numerous RNAs (protein-coding genes and non-coding RNAs) in the primary tumor tissue and the microenvironment serve a role in the chemotactic movement, colonization and destruction of bone tissue by cancer cells during PCa-induced bone metastasis (23-28). Bone metastasis occurs when tumor cells disrupt the physiological remodeling process through the same molecular mechanisms as those of bone precursors. This process involves molecular communication among bone cells, osteoblasts and osteoclasts. Tumor cells use bone tissue to absorb and release certain factors, thereby establishing a vicious cycle that promotes the establishing process (27). Exosomes, soluble substances and ligands that bind to the membrane affect the microenvironment of the bone marrow (22). Upon establishing certain conditions, a specialized environment is created that supports the survival of PCa cells, thereby facilitating the advancement of lesions toward a dominant state (22).

The present review summarizes the mechanism of action of protein-coding genes and non-coding RNAs in PCa-induced bone metastasis, discusses the value of applying the identified targets in the diagnosis and treatment of the disease, and provides novel ideas for the diagnosis and treatment of PCa-induced bone metastasis.

2. Protein-coding genes associated with bone metastases of PCa

Similar to other tumors, protein-coding genes serve an important role in regulating bone metastasis in PCa (22). By thoroughly examining the literature, it has been revealed that the bone metastasis of PCa is primarily influenced by the direct promotion of the spread to the bones of PCa, the interaction between PCa and bone tissue, the adhesion of PCa to bone tissue and the regulation of PCa by the bone microenvironment (22,29-31) (Table I). Through the aforementioned processes, most mRNAs participate in bone metastases and bone destruction after metastases of PCa (23,24,28,32-34). In addition, some mRNAs also have an inhibitory effect (35-38) (Fig. 1). Therefore, focusing on these molecules could potentially provide therapeutic benefits for PCa-induced bone metastasis.

Direct promotion of PCa metastases. Numerous studies have validated the contribution of protein-coding genes in facilitating the spread of PCa to the bones (23,24,29). Tetraspanin-18 (TSPAN18) (23), interferon induced transmembrane protein 3 (IFITM3) (24), fibroblast growth factor-inducible 14 (Fn14) (28), Frizzled 8 (FZD8) (32), T-Box protein 2 (TBX2) (33) and myc associated zinc finger protein (MAZ) (34) promote the migration and invasion of PCa cells by participating in Wnt/β-catenin, Ca (2+), TGF-β, NF-κB, kRas and other signaling pathways, and finally achieve the purpose of promoting PCa-induced bone metastasis.

TBX2, a member of the T-box family of transcription factors, has a critical function in embryonic development by acting as a negative regulator of the cell cycle inhibitor p21 (39). In human PCa specimens and human PCa xenograft mouse models, TBX2 expression was increased in bone metastases. *In vitro*, inhibiting the natural expression of TBX2 in PCa cell models could decrease the proliferation, formation of colonies and invasion of tumor cells. Inhibiting natural TBX2 in mouse xenografts of human PCa decreased the invasion of tumor cells and the spread of cancer to bones and soft tissues (33). In addition, blocking the endogenous TBX2 of PCa cells was found to reduce bone colonization in an intratibial mouse model (33). The study of the mechanism revealed that TBX2 is a downstream target of WNT3A, suggesting that the use of WNT3A antagonists could potentially serve as a novel medication for managing metastatic and skeletal issues in patients with PCa (33). Li *et al* (32) reported that FZD8 from the FZD family was highly expressed in bone metastatic PCa cell lines and tissues. Clinical tumor progression and bone metastases were positively associated with the elevated expression of FZD8. Furthermore, the excessive expression of FZD8 was observed to enhance the movement, infiltration and stem-like characteristics of PCa cells in laboratory settings through the activation of conventional Wnt/β-catenin signaling. Conversely, the inhibition of FZD8 resulted in the suppression of these characteristics. The suppression of FZD8 markedly reduced the occurrence of bone metastases *in vivo* in patients with PCa. Collectively, these observations revealed a novel process of bone spread in PCa and suggested that TBX2 and FZD8 could serve as promising targets for the treatment of PCa-induced bone metastasis.

Zhou *et al* (23) explored the regulatory mechanism of TSPAN18 promoting PCa-induced bone metastasis. The role of TSPAN18 in bone metastases of PCa was examined using both *in vitro* and *in vivo* models. The findings indicated that stromal interaction molecule 1 (STIM1) had a direct interaction with TSPAN18, and TSPAN18 competitively hindered the tripartite motif containing 32-mediated ubiquitination and degradation of STIM1, consequently enhancing the stability of the STIM1 protein. Furthermore, TSPAN18 effectively enhanced the influx of Ca(2+) in a STIM1-dependent manner, consequently leading to notable enhancement of the migration and invasion of PCa cells in laboratory settings and the development of bone metastases in animal experiments. This suggests that TSPAN18 may be an attractive therapeutic target to block PCa-induced bone metastasis. The presence of TGF-β in the bone matrix is a crucial factor in promoting bone metastases as it induces epithelial-mesenchymal transformation (EMT) (40). Liu *et al* (24) revealed that the activation of the TGF-β-Smads signaling pathway was facilitated by IFITM3 through its interaction with Smad4. This interaction was crucial in enhancing the proliferation, invasion and bone migration of PCa cells. Suppression of IFITM3 could impede the growth and movement of cells by reversing EMT and reducing the levels of transfer-associated substances such as fibroblast growth factors and parathyroid hormone-related protein. Microarray analysis revealed that the suppression of IFITM3 could modify the MAPK pathway linked to TGF-β-Smads signaling. The findings indicated that IFITM3 had a cancer-causing function in the progression of PCa and the spread of cancer to the bones via a novel pathway involving TGF-β, Smads and MAPK. Furthermore, Yin *et al* (28) reported that FN14, which belongs to the TNF receptor family, serves a role in enhancing bone metastases. In experimental models, loss of FN14 inhibited bone metastases, and FN14 could be functionally reconstituted through

Table I. Coding genes that regulate PCa-induced bone metastasis.

First author/s, year	Coding genes	Prognosis of patients with high expression of coding gene in tumor tissue	Regulation mechanism	Phenotypes	(Refs.)
Zhou *et al*, 2023	TSPAN18	Poor	TSPAN18 promotes Ca^{2+} inflow in a STIM1-dependent manner	Migration and invasion of PCa cells, and bone metastases *in vivo*	(23)
Liu *et al*, 2019	IFITM3	Poor	IFITM3 activates the TGF-β-Smads signaling pathway by binding to Smad4	PCa progression and bone metastases	(24)
Yin *et al*, 2014	FN14 (TNFRSF12A)	Poor	FN14 is involved in PCa metastasis via the NF-κB pathway	Bone metastases of PCa cells	(28)
Kolonin *et al*, 2017	RAGE and PR3	Poor	PR3 binds to RAGE on the surface of PCa cells and induces tumor cell motility by activating and phosphorylating a non-proteolytic signal transduction cascade of ERK1/2 and JNK1	PCa cells homing to the bone marrow	(30)
Li *et al*, 2017	FZD8	Poor	FZD8 activates the Wnt/β-catenin signaling pathway	Migration, invasion and stem-like phenotype of PCa cells	(32)
Nandana *et al*, 2017	TBX2	Poor	TBX2 works by promoting the transcription of WNT promoters	PCa bone metastases	(33)
Yang *et al*, 2019	MAZ	Poor	MAZ relies on the KRas signaling pathway for its function	Promotion of PCa bone metastases	(34)
Zhang *et al*, 2023	RBM3	Good	RBM3 upregulates catenin β1 mRNA methylation, resulting in decreased CTNNB1 mRNA stability and subsequent inactivation of the Wnt signaling pathway	Inhibition of the stemness remodeling of PCa cells by osteoblasts	(35)
Yamaguchi *et al*, 2022	Regucalcin	Good	Regucalcin blocks the production of TNF-α in PCa cells	Inhibition of the migration, invasion and bone metastases of human PCa cells	(37)
Wang *et al*, 2023	Spondin 2	Poor	Spondin 2 acts on the PI3K/AKT/mTOR pathway	Promotion of bone formation	(45)
Zhang *et al*, 2023	FBXO22	Poor	FBXO22 activates the NGF/TRKA pathway by degrading KLF4 in macrophages	PCa cell activity and osteogenic injury	(46)
Ziaee *et al*, 2014	RANKL	Poor	RANKL promotes PCa bone metastases via the NF-κB pathway	PCa bone metastases	(47)
Zhao *et al*, 2020	PSCA	Poor	PSCA functions via the NF-κB/integrin-α4 pathway	Adhesion of PCa cells to BMECs	(50)
Yan *et al*, 2014	DDR2	Poor	DDR2 is involved in Runx2 phosphorylation and TGF-β signaling	Osteoclast differentiation and bone resorption	(52)

Table I. Continued.

First author/s, year	Coding genes	Prognosis of patients with high expression of coding gene in tumor tissue	Regulation mechanism	Phenotypes	(Refs.)
Jin *et al*, 2015	Talin1	Poor	Phosphorylation of talin1 leads to activation of β1 integrin	Activation of PCa cell transfer potential	(54)
Tai *et al*, 2014	WISP-1	Poor	WISP-1 downregulates miR-126 expression through αvβ1 integrin, FAK and p38 signaling pathways	Migration of PCa cells	(56)
Chang *et al*, 2018	WISP-1	Poor	WISP-1 enhances the expression of VCAM-1 in PCa cells	Adhesion of cancer cells to osteoblasts	(57)
Choi *et al*, 2022	SIRT5	Good	SIRT5 inhibits the PI3K/AKT/NK-κB signaling pathway	PCa metastases from bone to other tissues	(59)
Siddiqui *et al*, 2022	GDF15	Poor	GDF15 activates osteoclastogenesis by producing CCL2 and RANKL from osteoblasts and recruiting osteoblasts	Promotion of the growth of PCa in bone	(60)

BMECs, bone marrow endothelial cells; CCL2, C-C motif chemokine ligand 2; FAK, focal adhesion kinase; KLF4, KLF transcription factor 4; miR, microRNA; NGF, nerve growth factor; PCa, prostate cancer; RANKL, receptor activator of NF-κB ligand; Runx2, RUNX family transcription factor 2; STIM1, stromal interaction molecule 1; TRKA, tropomyosin receptor kinase A; VCAM-1, vascular adhesion molecule-1.

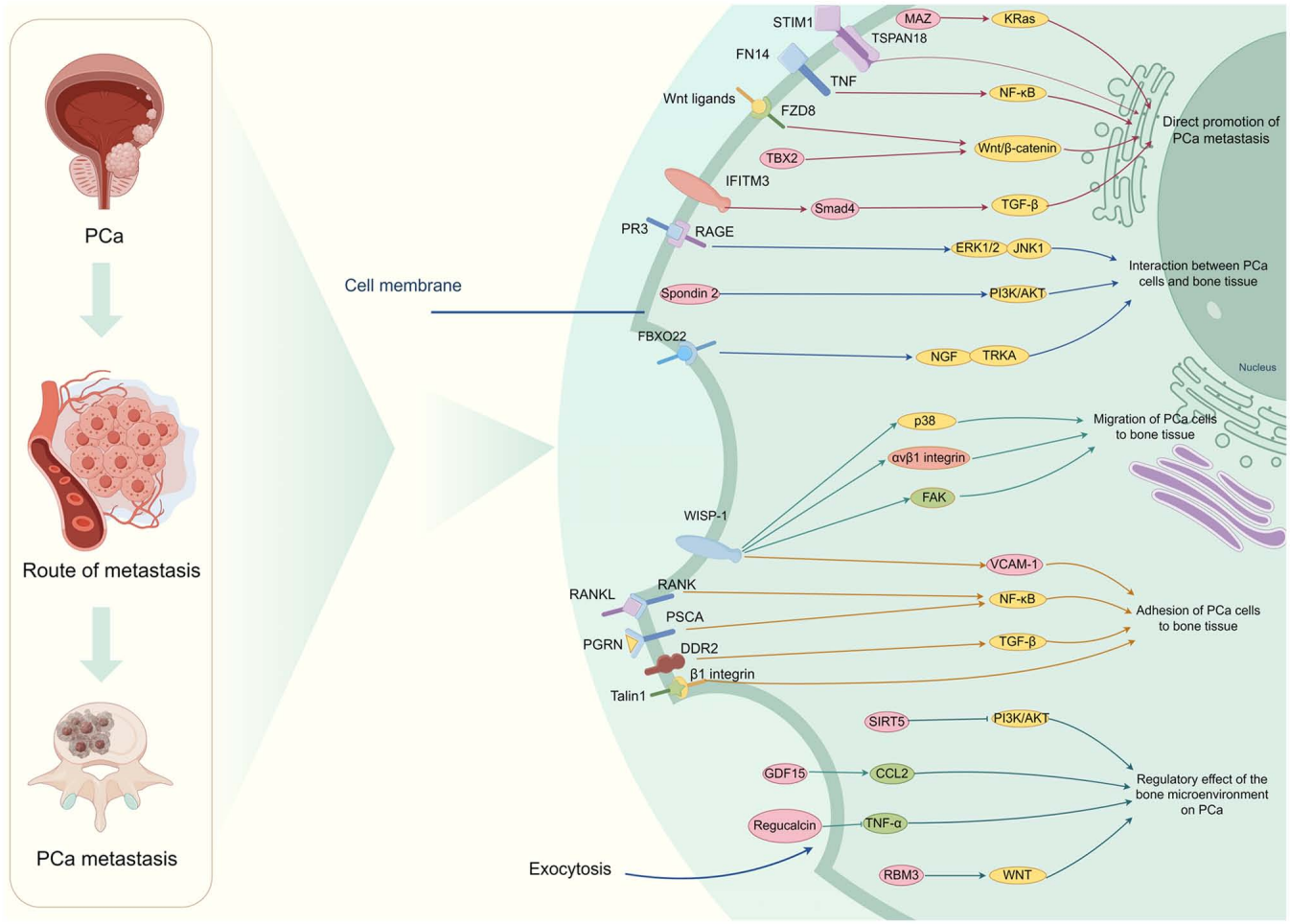

Figure 1. Mechanism of action of coding RNAs associated with bone metastasis in PCa. The image was generated by Figdraw (https://www.figdraw.com/static/index.html#/; 2.0 version; ID: POITW56400). PCa, prostate cancer.

IKβ-dependent NF-κB signaling activation. The results indicated that the NF-κB pathway served a role in the spread of PCa through FN14 signaling, highlighting FN14 as a potential treatment and imaging target for CRPC. MAZ, a zinc finger protein associated with Myc, has been extensively studied as an oncogene implicated in the advancement and spread of various types of cancer, including PCa (41-43). Yang *et al* (34) discussed the clinical significance and biological role of MAZ in bone metastases of PCa. The findings indicated that the level of MAZ expression was elevated in PCa cases with bone metastases compared with those without bone metastases. In patients with PCa, high expression of MAZ was negatively associated with both overall and bone metastasis-free survival. Enhancing the expression of MAZ enhanced the *in vitro* invasion and migration of PCa cells, whereas suppressing MAZ impeded the bone metastases of PCa cells *in vivo*. The findings additionally demonstrated that MAZ depends on kRas signaling pathways to enhance PCa-induced bone metastasis.

Mechanism of interaction between PCa and bone tissue. According to the latest research, ~85% of patients with PCa experience bone metastasis in the advanced stages (44); however, the underlying biological mechanism for this specific preference remains mostly unexplained. There is an interaction mechanism between PCa and bone tissue through some protein-coding genes. Kolonin *et al* (30) revealed that the connection between receptor for advanced glycation end products (RAGE) and protease 3 (PR3) facilitated the migration of PCa cells to the bone marrow. *In vitro*, PR3 interacted with RAGE on the surface of PCa cells, leading to the stimulation of tumor cell movement through the activation and phosphorylation of a non-proteolytic signaling pathway involving ERK1/2 and JNK1. Mouse tumor experiments validated that the abnormal expression of RAGE on human PCa cells was enough to facilitate the migration to the bone marrow temporarily. The results illustrated the role of RAGE-PR3 interactions in facilitating bone metastases during the progression of PCa in human cells, highlighting their potential impact on prognosis and therapeutic approaches. Spondin 2 is a specific diagnostic marker for PCa. Research has verified the function of spondin 2 in stimulating the development of bone-forming cells in PCa cells (45). Spondin 2 enhances the production of Osterix and RUNX family transcription factor 2 (RUNX2) in bone cells, and it facilitates bone creation via the PI3K/AKT/mTOR pathway during the advancement of prostate tumors (45). In addition, Zhang *et al* (46) deliberated the specific regulatory mechanism and biological role of E3 ubiquitin ligase F-box protein 22 (FBXO22) in the metastasis of PCa. FBXO22 was upregulated in PCa tissues compared with paracancerous tissues and metastatic bone

tissues compared with bone tissues without bone metastases. Downregulation of FBXO22 decreased bone metastases and M2-type polarization of macrophages in mice. The activity of PCa cells and osteoblasts was detected by co-culturing them with macrophages. Knockdown of FBXO22 inhibited tumor activity, while restoring the osteoblast capacity of promoting bone formation and remodeling. The findings indicated that FBXO22 enhanced the proliferation activity of PCa cells and caused osteogenic damage by inducing polarization of M2 macrophages.

Adhesion of PCa to bone tissue. Increased expression of RANKL in PCa cells can promote bone metastases of PCa (31). The molecular mechanisms of bone preference in PCa promote the growth and survival of PCa cells in the bone environment, as well as the recruitment of bystander dormant cells to participate in bone metastases (47). A study has confirmed the strong attachment of PCa cells to proteins within the bone matrix through the RANKL/receptor activator of NF-κB axes (47). PCa cells exhibit a tendency to stick to bone marrow endothelial cells (BMECs), leading to the formation of metastasis that preferentially targets the bone (48). Earlier data have indicated a higher tendency for metastases in PCa cells that express prostate stem cell antigen (PSCA) (49). Zhao *et al* (50) described the role of PSCA in the adhesion of PCa cells to BMECs. Cell adhesion was assessed by adhesion tests and transendothelial migration. The results confirmed that PSCA/progranulin (PGRN) promoted the adhesion and metastases of PCa cells to BMECs via the NF-κB/integrin-α4 pathway. The results indicated that targeting PSCA/PGRN could be a viable option for the treatment of the spread of PCa, particularly to the bones.

Collagen binding can activate discoidin domain receptor 2 (DDR2), which belongs to the receptor tyrosine kinase family (51). Yan *et al* (52) explored the role and mechanism of DDR2 in bone spread of PCa. The study found that enhanced DDR2 expression led to increased motility and aggressiveness of PCa cells, while knockdown of DDR2 by specific short hairpin RNAs (shRNAs) led to inhibition. Knockdown of DDR2 in PCa cells resulted in reduced proliferation, differentiation and function of osteoblasts. Animal models of bone metastases using intraosseous injection showed that DDR2 promoted osteolytic metastasis *in vivo*. According to molecular evidence, DDR2 serves a role in the activation of osteoclasts and the breakdown of bone vis TGF-β, thus facilitating the attachment of PCa cells to type I collagen (52). Adaptor proteins called talins control adhesion signals by connecting integrins to the cytoskeleton. Talins serve a crucial role in activating integrins by directly binding to them (53). Jin *et al* (54) revealed that the activation of β1 integrin in metastatic PCa cells leads to an increase in PCa metastases to both lymph nodes and bone. Their research has shown that the phosphorylation of talin1 by CDK5, resulting in the activation of β1 integrin, can enhance the metastatic capability of PCa cells.

Wnt-1-induced secreted protein 1 (WISP-1), a member of the cysteine rich angiogenic inducer 61, connective tissue growth factor, Nov family of matricellular proteins, has a crucial function in the development of bones (55). Tai *et al* (56) reported that introducing WISP-1 shRNA into osteoblasts reduced vascular adhesion molecule-1 (VCAM-1) expression and PCa migration. The study revealed that WISP-1, derived from osteoblasts, suppressed microRNA (miRNA/miR)-126 expression by utilizing αvβ1 integrin, focal adhesion kinase and p38 signaling pathways, which facilitated the movement of human PCa cells and enhanced the expression of VCAM-1 (56). Chang *et al* (57) revealed that WISP-1 controlled the process of bone mineralization by stimulating the production of BMP2, BMP4 and osteopontin in osteoblasts. WISP-1, derived from osteoblasts, increased the VCAM-1 expression in PCa cells, leading to the promotion of cancer cell adhesion to osteoblasts. Therefore, WISP-1 may be a novel molecular therapeutic target for PCa-induced bone metastasis.

Regulatory effect of the bone microenvironment on PCa. Metastasis of PCa to the bone can result in the induction of epigenome reprogramming and dry remodeling of cancer cells, consequently enhancing the adaptability of cancer cells to the bone microenvironment and potentially causing secondary tumor metastases (22). The interaction between PCa cells and the bone microenvironment establishes a harmful cycle that controls the bone microenvironment, enhances bone abnormalities and stimulates the growth of bone tumors (22). However, the molecular mechanism by which PCa regulates the bone microenvironment is complex. Prior research has validated that certain protein-coding gene molecules contribute to the control of the bone microenvironment, facilitating the proliferation of PCa within the skeletal system (58).

Some mRNAs are involved in the negative regulation of PCa progression in the bone microenvironment (35-37). Zhang *et al* (35) revealed that RNAs binding motif 3 (RBM3) disrupted CD44 alternative splicing, thereby influencing the stem-like characteristics of PCa. Methyltransferase 3 increased the methylation of N6-methyladenosine on catenin β1 mRNA, as induced by RBM3 (35). Furthermore, the expression of regucalcin impeded the migration and invasion of human PCa cells *in vitro*. It also resulted in reduced levels of Ras, Akt, MAPK, ribosomal S6 kinase 2, mTOR, caveolin-1 and integrin β1, which are crucial proteins for metastasis (36). Yamaguchi *et al* (37) reported that the excessive expression of regucalcin could hinder the generation of TNF-α. TNF-α may be an important mediator in the interaction between tumor cells and bone cells. The excessive expression of regucalcin had the ability to impede the movement, infiltration and spread of human PCa cells to the bones. The findings of this research offer a novel approach for the treatment of PCa-induced bone metastasis by focusing on regucalcin. Sirtuin 5 (SIRT5) is an NAD(+)-dependent deacylase that is considered a key regulator of multiple cancer types such as gastric cancer, colorectal cancer and clear cell renal cell carcinoma (38). The suppression of the PI3K/AKT/NK-κB pathway by SIRT5 has been observed to decrease when PCa metastasizes from the bone to other tissues (59). Furthermore, Siddiqui *et al* (60) investigated the role of growth differentiation factor-15 (GDF15) in the bone metastasis of advanced-stage PCa. Using preclinical mouse models and *in vitro* coculture systems, the study demonstrated that PCa-secreted GDF15 not only promoted bone metastases but also induced structural changes in the bone microenvironment. Mechanistically, GDF15 enhances osteoblast function and drives osteoclastogenesis by upregulating CCL2 and

RANKL, thereby facilitating PCa growth in the bone. These findings underscore the critical influence of GDF15 on the bone microenvironment and its contribution to PCa bone metastasis.

3. Non-coding RNAs associated with bone metastases of PCa

Approximately 98% of the human genome is considered to be transcribed into non-coding RNAs, which serve a crucial role in regulating gene expression at the epigenetic, transcriptional and post-transcriptional stages (61). The significance of non-coding RNAs in cancer is slowly being comprehended and has emerged as a crucial field of research focus. According to their size, they are mainly divided into miRNAs, long non-coding RNAs (lncRNAs) and circular RNAs. miRNAs, which are small RNA molecules that are 19-25 nucleotides long, control gene expression by blocking the translation of mRNA (62). Approximately 30% of the protein-coding genes within the human genome undergo regulation through the inherent expression of miRNAs. Therefore, the significance of miRNAs lies in their role in regulating cellular pathways linked to the development and advancement of PCa-induced bone metastasis (25) (Fig. 2). lncRNAs, which are longer than 200 nucleotides, serve a role in numerous biological processes such as enlisting transcriptional regulators, interacting with chromatin, controlling proteins and regulating epigenetics (63). They can also prevent targeted mRNA degradation by absorbing miRNAs as sponges in PCa (64) (Fig. 2). Exosomes consist of a range of diminutive compounds, such as non-coding RNAs, that are considered to have a strong association with the spread of PCa to the bones (65). In summary, non-coding RNAs have emerged as a subject of investigation, with multiple studies now indicating their involvement in PCa-induced bone metastasis (26,66-68) (Tables II and III).

miRNAs. Over the past decade, research has revealed that miRNAs serve a crucial role in the regulation of tumor progression and metastases. Research has additionally verified that miRNAs also control the progression of PCa-induced bone metastasis (66). Exosomes derived from PCa have been demonstrated to enhance events associated with metastasis, including the differentiation and proliferation of osteoblasts and osteoclasts. Dysregulated miRNA expression in PCa can potentially cause irregular bone restructuring and facilitate tumor growth (66). Research has verified that miR-375 (67), miR-1-3p/143-3p/145-5p (69), miR-409-3p/-5p (70), miR-210-3p (71), miR-141-3p (72), miR-532-3p (73) and additional factors contribute to the advancement of PCa-induced bone metastasis through epigenetic regulatory mechanisms (Table II). These miRNAs can promote or inhibit PCa-induced bone metastasis by acting on downstream target genes and finally regulating the signaling pathway of PCa-induced bone metastasis (Fig. 2).

The mechanism of action of the aforementioned miRNAs was studied. miR-375 directly targets disco interacting protein 2 homolog C and upregulates the Wnt signaling pathway, thus promoting the differentiation of human mesenchymal stem cells into osteoblasts. Furthermore, miR-375 facilitated the *in vitro* proliferation, invasion and migration of PCa cells, while also promoting tumor advancement and osteogenic metastasis *in vivo* (67). Experimental evidence has revealed that miR-1-3p/143-3p/145-5p enhanced the *in vitro* proliferation and migration of PCa. Interaction with β-catenin enabled LIM and SH3 protein 1 to serve as a shared target for these three miRNAs, potentially triggering the activation of the Wnt signaling pathway (69). Josson *et al* (70) confirmed the increased expression of miR-409-3p/-5p in bone metastatic PCa cell lines and PCa tissues of men with a high Gleason score. Elevated levels of miR-409-3p expression were associated with poor progression-free survival in patients with PCa. The research indicated that miR-409-3p/-5p serves a role in the biology of PCa by facilitating the growth of tumors, promoting EMT and causing bone metastases. PCa-induced bone metastasis is a well-known consequence of the constant activation of TGF-β signaling (70). Protein interacting with protein kinase C α (PRKCA) 1 (PICK1), the protein that interacts with PRKCA1, serves a crucial role in inhibiting the TGF-β pathway (70). Dai *et al* (71) confirmed that the excessive expression of miR-210-3p resulted in the reduction of PICK1 in PCa tissues that had spread to the bones. *In vitro*, exosomes facilitated the transfer of miR-141-3p to osteoblasts, subsequently enhancing osteoblast activity. Additionally, the protein level of target gene DLC1 Rho GTPase activating protein is suppressed by miR-141-3p, which serves a crucial role in the activation of the p38/MAPK pathway (71). Controlling the microenvironment of bone metastases is crucial for the development of bone metastases and osteogenic damage in PCa (72).

miR-210-3p is a widely studied cancer-causing miRNA that is linked to different aspects of cancer development, advancement and spread (74,75). A study revealed that miR-210-3p expression was higher in PCa tissues with bone metastases compared with those without bone metastases. In patients with PCa, there was a positive association between high expression levels of miR-210-3p and serum prostate-specific antigen (PSA) levels, Gleason grade and the presence of bone metastases. *In vitro*, enhancement of the EMT, invasion and migration of PCa cells was observed with the upregulation of miR-210-3p, whereas the inhibition of invasion and migration of PCa cells was observed with the silencing of miR-210-3p. The findings additionally indicated that miR-210-3p sustained continuous activation of NF-κB signaling in PCa cells (74). This is achieved by targeting TNFAIP3 interacting protein 1 and suppressor of cytokine signaling 1, which are negative regulators of NF-κB signaling, resulting in EMT, invasion, migration and bone metastases (74). Furthermore, miR-532-3p is a miRNA that serves a role in numerous aspects of cancer onset and spread (76). Overexpression of miR-532-3p inhibits activation of NF-κB signaling by simultaneously targeting tumor necrosis factor receptor-associated factor 1 (TRAF1), TRAF2 and TRAF4, thereby enhancing the invasion, migration and bone metastases of PCa cells (73). The results hold significance in diagnosing and treating bone metastases in the prostate, and miRNAs appear to be a promising focus for therapeutic intervention in PCa-induced bone metastasis.

In addition, some miRNAs have been found to serve an inhibitory role in regulating bone metastases of PCa. It has been confirmed that miR-145-5p (77), miR-1 (78), miR-335, miR-543 (79), miR-466 (80), miR-141-3p (81), miR-133b (82),

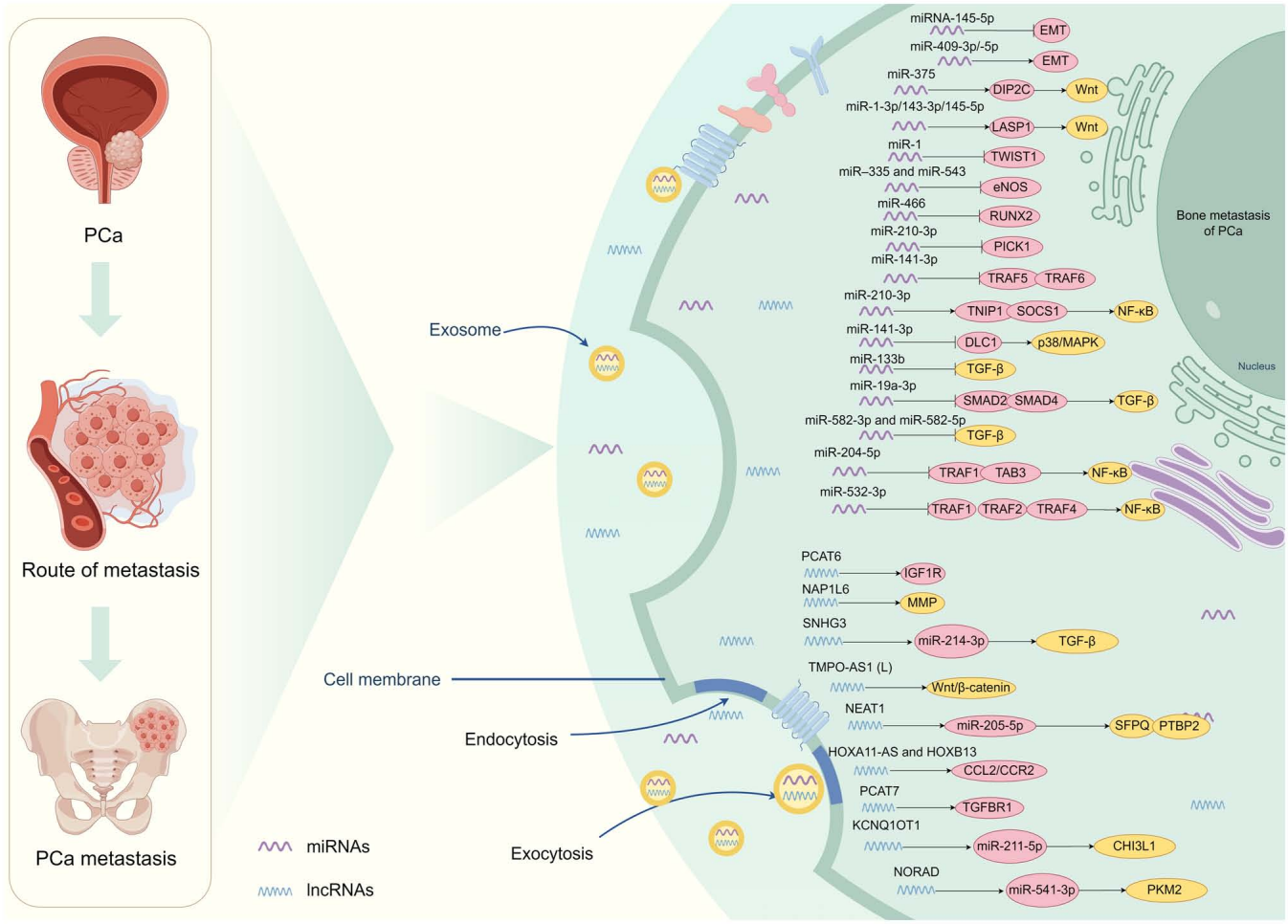

Figure 2. Mechanism of action of non-coding RNAs associated with bone metastasis in PCa. The image was generated by Figdraw (https://www.figdraw.com/static/index.html#/; 2.0 version; ID: PTATU24342). miRNA, microRNA; PCa, prostate cancer.

miR-582-3p, miR-582-5p (83) and miR-204-5p (84) inhibited PCa-induced bone metastasis as epigenetic regulatory mechanisms (Fig. 2). The specific regulatory mechanism has also been deeply studied.

Research has revealed that miR-145-5p has the ability to suppress the growth, movement and infiltration of PCa-induced bone metastasis. In PC3 cells, miR-145-5p suppressed the expression of basic fibroblast growth factor, insulin-like growth factor and TGF-β. The expression of E-cadherin, an epithelial marker, was enhanced by miR-145-5p, while the expression of MMP-2 and MMP-9 was reduced. miRNA-145-5p mediated EMT and induced apoptosis. miR-145-5p negatively regulated EMT, inhibited PCa-induced bone metastasis, and promoted apoptosis of PCa-induced bone metastasis cells (77). Conversely, Guo *et al* (69) identified its association with the regulation of LASP1, suggesting a context-dependent role that may facilitate bone metastasis in certain scenarios. These findings underscore the complex interactions of microRNA-145-5p in prostate cancer, highlighting its potential as a target for both diagnostic and therapeutic strategies in managing bone metastatic disease. miR-466 plays a significant role in inhibiting bone metastasis of PCa by directly regulating the osteogenic transcription factor RUNX2 (80). Research indicates that miR-466 targets RUNX2, leading to a downregulation of its expression, which subsequently impairs osteoblastic activity and tumor growth in the bone microenvironment. This regulatory mechanism contributes to the suppression of metastatic spread by altering key pathways associated with bone remodeling and cancer cell interactions with bone tissue (80). Therefore, miR-466 represents a potential therapeutic target for preventing bone metastasis in prostate cancer, providing insights into novel treatment approaches.

Huang *et al* (82) reported that low miR-133b expression was associated with the occurrence, progression and recurrence of PCa. By directly targeting TGF-β receptors I and II, miR-133b hindered the function of TGF-β signaling, consequently suppressing the bone metastases of PCa cells. Similarly, bone metastatic PCa tissues and cells exhibited decreased miR-19a-3p expression. Increased miR-19a-3p expression suppressed the *in vitro* invasion and migration of PCa cells, as well as the development of bone metastases *in vivo*. By contrast, silencing of miR-19a-3p had the opposite effect. The findings additionally showed that miR-19a-3p suppressed the ability of PCa cells to invade and migrate by targeting the downstream effectors SMAD2 and SMAD4 of the TGF-β pathway, leading to the deactivation of TGF-β signaling (85). Therefore, the results revealed a novel mechanism for the suppressive impact of miR-19a-3p on PCa-induced bone metastasis, thereby aiding the advancement of potent treatments for PCa. Furthermore, there was a notable association

Table II. Aberrantly expressed miRNAs regulate PCa-induced bone metastasis.

First author/s, year	miRNAs	Prognosis of patients with aberrantly expressed miRNAs in tumor tissues	Regulation mechanism	Phenotype	(Refs.)
Liu *et al*, 2023	miR-375	Poor	miR-375 targets DIP2C and activates the Wnt signaling pathway	miR-375 promotes osteoblast metastases and PCa progression	(67)
Guo *et al*, 2023	miR-1-3p/ 143-3p/145-5p	Poor	miR-1-3p/143-3p/145-5p acts on the LASP1 target and activates the Wnt signaling pathway by interacting with β-catenin	Promotes the proliferation and migration of PCa	(69)
Josson *et al*, 2014	miR-409-3p/-5p	Poor	miR-409-3p/-5p serves an important biological role by acting on tumor EMT	Promotes PCa growth and bone metastases	(70)
Dai *et al*, 2017	miR-210-3p	Poor	miR-210-3p expression leads to downregulation of PICK1	Promotes bone metastases of PCa	(71)
Ye *et al*, 2017	miR-141-3p	Poor	miR-141-3p decreases the protein levels of the target gene DLC1 and activates the p38/MAPK pathway	miR-141-3p promotes the activity of osteoblasts and regulates the bone metastasis microenvironment	(72)
Wa *et al*, 2020	miR-532-3p	Poor	miR-532-3p activates the NF-κB signaling pathway by targeting TRAF1, TRAF2 and TRAF4	miR-532-3p is a potential suppressor of bone metastasis in prostate cancer, as its upregulation inhibits invasion and migration	(73)
Ren *et al*, 2017	miR-210-3p	Poor	miR-210-3p maintains sustained activation of NF-κB signaling by targeting TNIP1 and SOCS1	miR-210-3p enhances bone metastasis in PCa by promoting EMT	(74)
Luo *et al*, 2022	miRNA-145-5p	Good	miRNA-145-5p negatively regulates EMT	miRNA-145-5p inhibits PCa bone metastases and promotes apoptosis of PCa bone metastases cells	(77)
Chang *et al*, 2015	miR-1	Good	miR-1 exerts its function by inhibiting the TWIST1 pathway	Inhibits bone metastases of PCa	(78)
Fu *et al*, 2015	miR-335 and miR-543	Good	miR-335 and miR-543 downregulate the expression levels of eNOS	Inhibits the migration and invasion of PCa	(79)
Colden *et al*, 2017	miR-466	Good	miR-466 directly targets the bone-associated transcription factor RUNX2	Inhibits the growth and metastasis of PCa	(80)
Huang *et al*, 2017	miR-141-3p	Good	miR-141-3p directly targets TRAF5 and TRAF6	Inhibits the invasion, migration and bone metastases of PCa cells	(81)
Huang *et al*, 2018	miR-133b	Good	miR-133b inhibits the activity of the TGF-β signaling pathway by directly targeting TGF-β receptors I and II	Inhibits the invasion and migration of PCa cells *in vitro* and bone metastases *in vivo*	(82)
Huang *et al*, 2019	miR-582-3p and miR-582-5p	Good	miR-582-3p and miR-582-5p inhibit TGF-β signaling pathways by targeting SMAD2, SMAD4, TGFBRI and TGFBRII	Inhibits the invasion and migration of PCa cells *in vitro* and bone metastases *in vivo*	(83)

Table II. Continued.

First author/s, year	miRNAs	Prognosis of patients with aberrantly expressed miRNAs in tumor tissues	Regulation mechanism	Phenotype	(Refs.)
Wa *et al*, 2019	miR-204-5p	Good	miR-204-5p inhibits NF-κB signaling by targeting TRAF1, TAB3 and MAP3K3	Inhibits PCa cell invasion, migration and bone metastases	(84)
Wa *et al*, 2018	miR-19a-3p	Good	miR-19a-3p causes TGF-β signaling inactivation by targeting SMAD2 and SMAD4	Invasion and migration of PCa cells are inhibited	(85)

DIP2C, disco interacting protein 2 homolog C; DLC1, DLC1 Rho GTPase activating protein; EMT, epithelial-mesenchymal transformation; eNOS, endothelial nitric oxide synthase; LASP1, LIM and SH3 protein 1; miRNA/miR, microRNA; PCa, prostate cancer; PICK1, protein interacting with PRKCA 1; RUNX2, RUNX family transcription factor 2; SOCS1, suppressor of cytokine signaling 1; TAB3, TGF-β activated kinase 1 (MAP3K7) binding protein 3; TGFBR, TGF-β receptor; TNIP1, TNFAIP3 interacting protein 1; TRAF, tumor necrosis factor receptor-associated factor; TWIST1, twist family bHLH transcription factor 1.

between decreased levels of miR-582-3p and miR-582-5p and more advanced clinicopathological characteristics, as well as a shorter duration of bone metastases-free survival in patients with PCa. *In vitro*, the invasion and migration of PCa cells were suppressed by the increased expression of miR-582-3p and miR-582-5p, which also hindered bone metastases *in vivo*. The findings indicated that miR-582-3p and miR-582-5p reduced the severity of PCa-induced bone metastasis by suppressing the TGF-β pathway. The authors achieved this by targeting multiple elements of TGF-β signaling, such as SMAD2, SMAD4, TGF-β receptor I (TGFBRI) and TGFBRII (83).

Multiple cancer types, including breast cancer, osteosarcoma and gastric cancer, have been found to involve the participation of miR-204-5p in their development and spread, where miR-204-5p functions as a tumor suppressor by targeting specific oncogenes (86-88). Wa *et al* (84) found that miR-204-5p expression was decreased in PCa tissues and serum samples with bone metastases compared with those without bone metastases, which was related to the late clinicopathological features of patients with PCa and the poor survival rate without bone metastases. Furthermore, under laboratory conditions, the increase in miR-204-5p expression hindered the movement and infiltration of PCa cells. Notably, the enhancement of miR-204-5p expression suppressed the spread of PCa cells to the bones when tested *in vivo*. The findings additionally indicated that miR-204-5p hindered the infiltration, movement and bone spread of PCa cells by targeting TRAF1, TGF-β activated kinase 1 (MAP3K7) binding protein 3 and MAP3K3, deactivating the NF-κB pathway. The research revealed a novel functional role of miR-204-5p in the spread of PCa to the bones and highlighted the possible significance of miR-204-5p as a serum biomarker for diagnosing PCa-induced bone metastasis. Furthermore, miR-141-3p has been extensively studied as a miRNA in cancer, and the decrease in miR-141-3p levels has been extensively documented to serve a role in the advancement and spread of various types of human cancer, including colorectal cancer and renal cell carcinoma (89,90). Huang *et al* (81) found that miR-141-3p expression was decreased in bone metastatic PCa tissues compared with non-bone metastatic PCa tissues. There was a positive association between the reduced expression of miR-141-3p and the serum PSA level, Gleason grade, and bone metastases status in patients with PCa. Furthermore, overexpression of miR-141-3p suppressed the process of EMT, as well as the invasion and migration of PCa cells in experimental settings. An *in vivo* reduction of bone metastases in PC-3 cells was observed with the upregulation of miR-141-3p. By directly targeting TRAF5 and TRAF6, miR-141-3p hindered the activation of NF-κB signaling, consequently suppressing the invasion, migration and bone metastases of PCa cells.

lncRNAs. lncRNAs serve as crucial controllers of gene expression and contribute to the initiation and progression of tumors (91). Mounting evidence suggests that lncRNAs serve a role in the progression of PCa-induced bone metastasis. Due to its special growth environment and biomechanical properties, bone has become the preferred growth site of PCa (92-98). Identifying novel molecular entities that could potentially function as an initial indicator of the metastasis procedure may provide an opportunity to establish innovative

Table III. Aberrantly expressed lncRNAs regulate bone metastases in PCa.

First author/s, year	lncRNAs	Prognosis of patients with aberrantly expressed lncRNAs in tumor tissues	Regulation mechanism	Phenotype	(Refs.)
Lang *et al*, 2021	PCAT6	Poor	PCAT6 upregulates the expression of IGF1R by targeting the IGF2BP2/IGF1R RNA-protein three-dimensional complex	Promotes bone metastases of PCa.	(26)
Zheng *et al*, 2023	NAP1L6	Poor	NAP1L6 interacts with YY1 to promote transcription of MMP2 and MMP9 and activate the MMP signaling pathway	Promotes PCa cell migration, invasion and EMT	(68)
Wang *et al*, 2023	TMPO-AS1 (L)	Poor	TMPO-AS1 (L) activates the Wnt/β-catenin signaling pathway by enhancing the interaction between CSNK2A1 and DEAD-box helicase	Promotes the proliferation of bone marrow in PCa	(92)
Xi *et al*, 2022	SNHG3	Poor	SNHG3 enhances TGFBR1 expression and activates the TGF-β signaling pathway by targeting miR-214-3p	SNHG3 promotes bone metastasis in PCa, suggesting its potential as a biomarker and therapeutic target	(93)
Misawa *et al*, 2021	HOXA11-AS and HOXB13	Poor	HOXA11-AS and HOXB13 regulate the CCL2/CCR2 cytokine and integrin signaling pathways via autocrine and paracrine pathways	Promotes PCa metastases	(94)
Lang *et al*, 2020	PCAT7	Poor	PCAT7 upregulates TGFBR1 expression by adsorption of miR-324-5p	Overexpression of PCAT7 promotes PCa bone metastases *in vivo*, and migration, invasion and EMT of PCa cells *in vitro*	(95)
Hao *et al*, 2021	KCNQ1OT1	Poor	KCNQ1OT1 upregulates CHI3L1 expression via competitive binding to miR-211-5p	Promotes PCa progression	(96)
Hu *et al*, 2021	NORAD	Poor	NORAD may act as a ceRNA of miR-541-3p to promote PKM2 expression	Enhances the progression of PCa bone metastases	(97)
Mo *et al*, 2021	NEAT1	Poor	NEAT1 enhances RUNX2 expression by competitively interacting with miR-205-5p	NEAT1 promotes osteogenic differentiation of hBMSCs in PCa	(98)

CCL2, C-C motif chemokine ligand 2; CCR2, C-C motif chemokine receptor 2; ceRNA, competing endogenous RNA; CHI3L1, chitinase 3 like 1; CSNK2A1, casein kinase 2α1; EMT, epithelial-mesenchymal transformation; hBMSCs, human bone marrow-derived mesenchymal stem cells; IGF1R, insulin like growth factor 1 receptor; IGF2BP2, insulin like growth factor 2 mRNA binding protein 2; lncRNA, long non-coding RNA; miR, microRNA; PCa, prostate cancer; PKM2, pyruvate kinase M1/2; RUNX2, RUNX family transcription factor 2; TGFBR1, transforming growth factor β receptor 1; YY1, YY1 transcription factor.

and improved therapies and diagnostics. Research has established that PCAT6 (26), NAP1L6 (68), TMPO-AS1 (L) (92), SNHG3 (93), HOXA11-AS (94), PCAT7 (95), kcnq10t1 (96), NORAD (97), NEAT1 (98) and other similar lncRNAs contribute to the spread of PCa to the bones (Table III). These lncRNAs regulate the signaling pathway of PCa-induced bone metastasis by acting on downstream target genes, thus promoting PCa-induced bone metastasis (Fig. 2).

Lang *et al* (26) reported that PCAT6 expression was increased in PCa tissues that had spread to the bones, and a high level of PCAT6 expression was indicative of a poor prognosis for patients with PCa. *In vitro*, functional experiments demonstrated inhibition of invasion, migration and proliferation of PCa cells, along with suppression of bone metastases and tumor growth *in vivo*, following knockdown of PCAT6. PCAT6 promoted the bone metastases of PCa by upregulating the expression of insulin like growth factor 1 receptor (IGF1R) through the insulin like growth factor 2 mRNA binding protein 2/IGF1R RNA-protein three-dimensional complex, which enhanced the stability of IGF1R mRNA. PCAT6 shows potential as an indicator and a focus for addressing PCa-induced bone metastasis. Zheng *et al* (68) detected the expression of NAP1L6 in PCa cells by reverse transcription-quantitative PCR, and found that NAP1L6 was upregulated in PCa cells. Cell migration, invasion and EMT were found to be suppressed by the silencing of NAP1L6 in functional experiments, whereas the overexpression of NAP1L6 enhanced cell migration, invasion and EMT. The study also employed co-immunoprecipitation, luciferase reporter gene assays and RNA immunoprecipitation to determine the potential regulatory mechanism of NAP1L6. The interaction between NAP1L6 and YY1 transcription factor enhanced the transcription of MMP2 and MMP9, thereby activating the MMP signaling pathway. In summary, NAP1L6 functions as a cancer-causing gene in PCa, indicating that targeting NAP1L6 could be a promising approach for the treatment of PCa. Wang *et al* (92) revealed that the levels of long transcript of TMPO-AS1 were increased in PCa tissues with bone metastases. Furthermore, upregulation of TMPO-AS1 (L) was associated with advanced clinicopathological features and reduced bone metastasis-free survival in patients with PCa. The mechanism assays of the study demonstrated that TMPO-AS1 (L) could act as a framework to boost the connection between casein kinase 2α1 and DEAD-box helicase, leading to the activation of the Wnt/β-catenin signaling pathway. Consequently, this activation promotes myelodysplasia in PCa. TMPO-AS1 (L) has been recognized as a potential prognostic indicator and therapeutic target for PCa-induced bone metastasis.

PCa-induced bone metastasis is closely related to tumor death (13). The involvement of SNHG3, a lncRNA host gene, has been linked to the onset and progression of various types of human malignancies, including breast cancer (99), osteosarcoma (100) and gastric cancer (101). Higher expression of SNHG3 was observed in PCa tissues with positive bone metastases compared with PCa tissues with negative bone metastases and adjacent normal tissues. Patients with PCa who exhibited high levels of SNHG3 were likely to have advanced clinicopathological characteristics and a poor prognosis. Simultaneously, suppressing SNHG3 hindered the growth, movement and infiltration of PCa cells, and impeded the spread of PCa cells to the bones. Functionally, SNHG3 boosted TGFBR1 expression and triggered the TGF-β signaling pathway through targeting of miR-214-3p. These findings indicated that SNHG3 could potentially serve as a biomarker and a promising target for therapeutic interventions in PCa (93). Similarly, Misawa *et al* (94) reported that the overexpression of lncRNA HOXA11-AS facilitated the invasion and proliferation of PC3 PCa cells. HOXA11-AS regulated the bone metastases-associated C-C motif chemokine ligand 2 (CCL2)/C-C motif chemokine receptor 2 (CCR2) signaling pathway in PC3 PCa cells and SaOS2 osteoblasts. In both autocrine and paracrine manners, HOXA11-AS facilitated the metastases of PCa by controlling the cytokine CCL2/CCR2 and integrin signaling pathways. Through the examination of a dataset from The Cancer Genome Atlas, it was revealed that PCAT7 is a lncRNA linked to bone metastases (95). Additionally, PCAT7 expression was elevated in bone metastases of primary PCa, which was associated with the condition of bone metastases and unfavorable prognosis among patients with PCa. Mechanistically, PCAT7 activates TGF-β/SMAD signaling by upregulating TGFBR1 expression by sponging miR-324-5p, thereby promoting PCa-induced bone metastasis. The findings of the study suggested that targeting PCAT7 could be a promising approach to treat PCa-induced bone metastasis by interfering with the functional interaction between PCAT7 and the TGF-β signaling pathway. Hao *et al* (96) revealed that lncRNA *KCNQ1OT1* expression was increased in both PCa tissues and cells. Inhibiting the expression could suppress the invasion, growth and spread of PCa cells. miR-211-5p competitively bound to KCNQ1OT1, and the CHI3L1 3'-untranslated region is the target of miR-211-5p. lncRNA KCNQ1OT1, as a competing endogenous RNA, upregulated CHI3L1 and promoted PCa progression by competitively binding to miR-211-5p. Hu *et al* (97) reported that NORAD was expressed highly in PCa tissues and cell lines, especially in bone metastases. Knockdown of the NORAD gene led to a decrease in the secretion and uptake of extracellular vesicles (EVs), as well as the inhibition of PCa cell growth, movement and spread to the bones. The study demonstrated that NORAD interacted with miR-541-3p, resulting in upregulation of PKM2. The transfer of PKH67-labeled EVs to bone marrow stromal cells was enhanced by the enforced expression of PKM2. NORAD can function as a competing endogenous RNA for miR-541-3p, enhancing PKM2 expression and consequently facilitating the progression of PCa-induced bone metastasis. This mechanism promotes the internalization and metastases of cancer cell-derived EVs, offering a novel perspective for the management of this condition. Mo *et al* (98) reported that PCa cells released exosomes that contained a type of RNA called NEAT1. The authors also found that NEAT1 had an impact on the process of osteogenic differentiation in human bone marrow-derived mesenchymal stem cells (hBMSCs) within the context of PCa. The NEAT1 molecule is transported into hBMSCs through exosomes derived from PCa cells. In both *in vivo* and *in vitro* settings, NEAT1 enhances RUNX2 expression by competitively interacting with miR-205-5p, and it also controls splicing factor proline and glutamine rich/polypyrimidine tract binding protein 2 to promote the osteogenic differentiation of hBMSCs.

4. Utilization of targeted diagnosis in bone metastases of PCa

Advances in molecular-targeted modular design for *in vivo* imaging applications have made it possible to study deep molecular interactions noninvasively and dynamically. PSMA PET/CT, a technology that specifically targets PSMA, has been increasingly utilized for the diagnosis of PCa and has shown promising therapeutic outcomes (102,103). Additionally, PSMA PET/CT exhibits notable benefits in detecting PCa-induced bone metastasis (104). Currently, bone scanning (BS) is the predominant technique employed for the early evaluation of PCa-induced bone metastasis (105), and is an imaging method that exhibits high sensitivity but low specificity (106). Extensive studies have been conducted to investigate the efficacy of 68Ga-PSMA PET/CT in identifying cancerous bone lesions and to determine its superiority over current bone imaging techniques (107-109). Furthermore, a study has revealed a higher diagnostic accuracy of PSMA-PET/CT in detecting PCa-induced bone metastasis compared with BS (110). Similarly, Pyka *et al* (19) compared the diagnostic efficacy of 68Ga-PSMA PET and (99m) Tc bone imaging for PCa-induced bone metastasis. In this retrospective analysis, the diagnostic efficacy of these approaches was evaluated in 126 individuals diagnosed with PCa. The findings of the study indicated that Ga-PSMA PET outperformed planar BS in identifying the affected bone region and assessing the overall bone participation in patients with PCa. In addition, a systematic analysis was conducted to investigate the diagnostic significance of 68Ga-PSMA PET/CT in detecting PCa-induced bone metastasis (111). An analysis of 37 research papers revealed that 68Ga-PSMA PET/CT revealed a greater number of lesions compared with bone imaging. Specifically, the diagnostic effectiveness for metastatic CRPC (mCRPC) was enhanced compared with bone imaging. The findings suggest that the use of 68Ga-PSMA PET/CT holds great potential in the detection of PCa.

Dynamic interactions among metastatic cancer cells, the cellular components of the bone marrow microenvironment (osteoblasts, osteoclasts and osteocytes) and bone stroma regulate the process of bone metastases (112). In the past few years, there has been a focus on the identification of EVs and their various functions in the regulation of PCa metastasis. Multiple research studies have demonstrated that interactions facilitated by EVs between cancer cells and the microenvironment of the bone effectively enhanced pathological bone metabolism at sites where metastasis occurs (113,114). miRNAs transmitted through EVs in the serum of patients were identified as a marker for PCa-induced bone metastasis (115). Wang *et al* (115) identified four prospective EV-delivered miRNAs, including miR-181a-5p, using miRNA deep sequencing and a miRNA microarray, and their expression in the bone metastases group was significantly higher than that in the non-bone metastases group ($P<0.05$). The diagnostic association between candidate miR-181a-5p and bone metastases was evaluated by logistic regression analysis, and the results showed that miR-181a-5p was associated with bone metastases of PCa. miR-181a-5p expressed by EVs is expected to be a diagnostic marker for bone metastases of PCa. Additionally, it has been identified that PCa exosomes are key mediators in regulating bone homeostasis, leading to osteoclastic lesions, and thus, promoting bone tumor growth (116). miR-92a-1-5p downregulates type I collagen expression by directly targeting COL1A1, which leads to the promotion of osteoclast differentiation and the inhibition of osteoblast generation (116). Wang *et al* (117) reported that EVs derived from tumors, which contained miR-378a-3p, had an impact on the spread of PCa to the bones. These EVs triggered the progression of bone destruction by activating the dual specificity tyrosine phosphorylation regulated kinase 1A/nuclear factor of activated T cells 1/angiopoietin like 2 pathway in bone marrow macrophages. Therefore, miR-378a-3p holds promise as a potential indicator for the spread of PCa. Treating PCa metastasis could potentially involve strategies such as decreasing the secretion of EVs containing miR-378a-3p or impeding the incorporation of miR-378a-3p into EVs. In addition, Zeng *et al* (118) first revealed that miR-18a-5p was upregulated within the bone microenvironment of individuals with bone metastases caused by PCa. Additional research revealed that miR-18a-5p was transmitted to osteoblasts through exosomes derived from PCa cells. Subsequently, it specifically affected the Hist1h2bc gene, leading to an increase in Ctnnb1 expression in the Wnt/β-catenin signaling pathway. Therefore, miR-18a-5p derived from exosomes may serve as a diagnostic indicator for bone metastases of PCa (118).

5. Utilization of targeted therapy in bone metastases of PCa

More than half of the patients with advanced PCa will develop bone metastases, and current treatment options are only aimed at the control of clinical symptoms, rather than a fundamental cure (119). Currently, the primary focus of clinical diagnosis and treatment is the development of novel targeted medications and the mitigation of bone-related occurrences, considering the difficulties encountered in managing PCa-induced bone metastasis (Table IV) (120). These mechanism studies indicate that PCa cells and bone tissue-related molecules are expected to be novel targets for anti-PCa-induced bone metastasis (121-123). Research has indicated that denosumab has the ability to decrease bone frailty and postpone the advancement of bone metastases in the prostate (124). Promising outcomes have also been observed in clinical trials for bone metastatic PCa when examining tyrosine kinase inhibitors such as cabozantinib (NCT01522443) (125) and dasatinib (NCT00918385) (126). Furthermore, atlacetam, a blocker of endothelin-A receptor, has been identified to decrease PSA levels and the occurrence of bone pain in individuals with metastasis (127). Therefore, targeted therapy of bone metastases of PCa has great potential.

In the past few years, choosing targeted therapy according to the tumor metastasis mechanism has emerged as a novel option in the realm of tumor treatment. This approach not only offers effective tumor eradication but also minimally affects normal cells (128). Genetic testing of patients with PCa with bone metastases is critical to find appropriate targeted therapies based on the specific molecular characteristics of each patient (129). The successful response to anti-programmed cell death protein 1 (PD-1) antibody therapy in certain patients with PCa is largely attributed to underlying characteristics such as defective mismatch repair mechanisms and the presence of microsatellite

Table IV. Clinical research on targeted therapy of mCRPC.

First author/s, year	Target	Interventions	Phases	No. of patients included	Main conclusions	(Refs.)
Mizuta *et al*, 2023	RANKL	Denosumab	Retrospective cross-sectional study	496	Denosumab effectively reduces skeletal-related events in patients with bone metastases from solid tumors.	(124)
Agarwal *et al*, 2022	MET and VEGFR	Cabozantinib	1b	132	Cabozantinib combined with atezolizumab shows a 23% objective response rate in mCRPC, indicating potential effectiveness.	(125)
Yu *et al*, 2009	Tyrosine kinase	Dasatinib	2	47	Dasatinib exhibits activity and reasonable tolerability in chemotherapy-naive patients with mCRPC involving bone metastasis.	(126)
Narayan*et al*, 2022	PSMA	PSMA-targeting CAR T cells	1	18	PSMA-targeting CAR T cells show promising efficacy in treating castration-resistant PCa with bone metastases.	(138)
Almuradova *et al*, 2024	PSMA	Lutetium-177 PSMA-617 radioligand therapy	2	165	Lutetium-177 PSMA-617 radioligand therapy reduces PSA levels and improves survival in patients with mCRPC.	(139)
Khreish *et al*, 2022	PSMA	177Lu-PSMA-617 RLT	3	254	177Lu-PSMA-617 RLT is associated with improved biochemical disease control and OS in the treatment of mCRPC.	(142)
Sweeney *et al*, 2021	AR/AKT	Ipatasertib plus abiraterone and prednisolone	3	1,611	Ipatasertib plus abiraterone improves radiographical progression-free survival.	(149)
Fizazi *et al*, 2011	RANKL	Zoledronic acid/ denosumab	3	1,904	Denosumab is better than zoledronic acid for prevention of skeletal-related events.	(150)
Shenderov *et al*, 2021	PD-1 and-4 CTLA	Ipilimumab/ nivolumab/ enzalutamide	2	30	Nivolumab plus ipilimumab exhibits only modest activity in patients with mCRPC.	(151)
Graff *et al*, 2020	PD-1	Pembrolizumab with enzalutamide	2	28	Pembrolizumab has activity in mCRPC when added to enzalutamide.	(152)
McNeel *et al*, 2022	PD-1	MVI-816 and pembrolizumab	2	25	PD-1 blockade combined with MVI-816 can augment tumor-specific T cells, and can result in a favorable 6-month disease control rate.	(153)

The included clinical studies are randomized controlled and retrospective clinical studies of targeted therapy for bone metastasis of PCa. AR, androgen receptor; CTLA-4, cytotoxic T-lymphocyte associated protein 4; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PCa, prostate cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PSA, prostate-specific antigen; RANKL, receptor activator of NF-κB ligand; SRE, skeleton-related event.

instability (130). However, a study confirmed that the CDK12 mutant cell line also showed a good response against PD-1 treatment (131). Individuals diagnosed with mCRPC exhibit resistance to androgen receptor (AR) inhibitors and androgen synthesis inhibitors, rendering them suitable candidates for targeted therapy involving poly ADP-ribose polymerase (PARP) inhibitors (132). Studies have shown that the PARP inhibitors used are olaparib or lucaparib, which are particularly effective in PCa cases associated with BRCA1/2 mutations and homologous recombination deficiencies (132,133). PARP inhibitor has shown effectiveness in treating cancer cells with homologous recombination defects that can be affected by alterations in base excision repair pathways (134).

Because of its specific expression in PCa, PSMA is not only an important diagnostic tool for bone metastases of PCa, but also a therapeutic target for patients with metastatic PCa (135,136). Numerous studies have focused on PSMA antibody-drug conjugates and PSMA-targeted chimeric antigen receptor therapy as potential treatments for CRPC (137,138). Lutetium-177-PSMA has emerged as a valuable treatment for mCRPC. Recent studies have demonstrated its ability to selectively target PSMA expressed on mCRPC cells, delivering targeted radiotherapy that effectively reduces the tumor burden (139,140). In clinical trials, Lutetium-177-PSMA has shown promising efficacy, leading to improvements in overall survival and quality of life of patients with mCRPC (141,142). This targeted approach not only enhances treatment outcomes but also minimizes damage to surrounding healthy tissue, marking an advancement in mCRPC therapy. PSMA BiTE, a builder of bispecific antibodies targeting CD3 and PSMA, redirects and activates T cells towards PSMA-expressing cells. This treatment has also been utilized for other malignancies, such as kidney cancer and melanoma, showing promising outcomes in these tumors as well as in PCa (143). Clinical trials are currently evaluating three additional participants in bispecific T cell therapy, namely glypican-1, disintegrin and metalloproteinase 17, and prostatic six transmembrane epithelial antigen 1 (144,145). Blocking the interactions between MDM2 and p53 to activate tumor suppressors is a promising target for mCRPC due to the role of TP53 inactivation in second-generation anti-androgen resistance and neuroendocrine differentiation (146). Idasanutlin is currently undergoing several clinical trials. It targets cell lines altered by p53, which, in the case of PCa, along with alterations in RB transcriptional corepressor 1, leads to castration-resistant, aggressive tumors with a poor prognosis (147). Future investigations should examine the effectiveness of idasanutlin in various hematological malignancies, analyzing the tumor response, biomarkers for treatment efficacy and potential resistance mechanisms. This research is vital for informing upcoming clinical trials and optimizing therapeutic strategies for patients with hematological malignancies and PCa.

Due to the significance of AKT in the PI3K pathway, the effectiveness of PI3K inhibitors in treating PCa-induced bone metastasis has been limited, resulting in only a partial response observed in the initial clinical trial (148). ATP-competitive inhibitors such as ipatasertib or capivasertib (NCT04404140 and NCT04087174), as well as allosteric inhibitors such as perifosine or MK-2206 (NCT00060437 and NCT00058214), are among the AKT inhibitors currently being tested in clinical trials. In a phase 2 trial, ipatasertib showed some degree of prolongation of the progression-free interval (NCT03072238) (149). An ongoing clinical trial is currently investigating the use of docetaxel and capivasertib in combination (NCT05348577). Radiology confirmed that the combination of ipavasertib and abiraterone improved progression-free survival (149). However, several studies are needed before it can be incorporated into clinical practice as a treatment option for PCa.

Targeted therapies have shown promise in the treatment of mCRPC, particularly in reducing bone metastases. A pivotal study by Fizazi *et al* (150) compared denosumab with zoledronic acid for managing bone metastases in men with CRPC. The findings revealed that denosumab delayed skeletal-related events, highlighting its effectiveness in preventing complications associated with bone metastases. Furthermore, recent trials, such as the one led by Shenderov *et al* (151), which explored the combination of nivolumab and ipilimumab with enzalutamide in patients expressing AR-variant 7, have demonstrated moderate activity. These results underscore the capability of targeted therapies to modulate the immune response and directly affect cancer progression in the bone microenvironment.

Further advancements have been made with combination therapies, demonstrating the feasibility and clinical potential of integrating immune checkpoint inhibitors such as pembrolizumab with traditional AR inhibitors. Graff *et al* (152) reported that the combination not only improved treatment outcomes but also presented a manageable safety profile in patients previously progressing on enzalutamide alone. Additionally, the work of McNeel *et al* (153) on T-cell activation using MVI-816 alongside pembrolizumab provided evidence for the role of targeted immunotherapy in enhancing antitumor responses. Overall, these clinical studies collectively reflect the effectiveness and safety of targeted therapies in managing bone metastases in mCRPC, paving the way for innovative treatment strategies that could ultimately improve the survival and quality of life of patients.

Furthermore, AR inhibitors remain a cornerstone in the treatment of mCRPC, particularly in cases involving bone metastases (154). Clinical studies, such as the results from the SPARTAN and PROSPER trials, have demonstrated that AR inhibitors, including apalutamide and enzalutamide, improve overall survival and delay disease progression in patients with mCRPC (155). These agents block the AR signaling pathway, which is crucial for the growth and survival of PCa cells, even in castration-resistant settings (156). Furthermore, investigations have shown that combining AR inhibitors with other therapies, such as radiopharmaceuticals and immunotherapy, may enhance treatment efficacy, further bolstering their role in managing mCRPC with bone metastases (152,157). As a result, AR inhibitors continue to be integral to both first-line and subsequent treatment strategies, promoting improved outcomes and extending survival of patients with this aggressive disease.

6. Discussion

Most patients with advanced PCa inevitably face the development of bone metastases. Conventional treatments for patients

with PCa-induced bone metastasis have limited efficacy (158). Gaining knowledge regarding the molecular process of PCa-induced bone metastasis is beneficial for the advancement of novel targeted approaches for the diagnosis and treatment of this disease. Research has indicated that numerous protein-coding genes (TSPAN18, IFITM3, Fn14, FZD8, TBX2 and MAZ) and non-coding RNAs [miR-375, miR-1-3p/143-3p/145-5p, miR-409-3p/-5p, miR-210-3p, miR-141-3p, miR-532-3p, PCAT6, NAP1L6, TMPO-AS1(L), SNHG3, HOXA11-AS, PCAT7, kcnq10t1, NORAD and NEAT1] serve crucial roles in controlling the advancement of PCa-induced bone metastasis (23,24,26,28, 32-34,67-73,92-98). These molecules control various substances and ultimately contribute to the progression of tumors through well-known tumor pathways, such as the Wnt/β-catenin (32), TGF-β (24), NF-κB (28) and kRas (34) pathways.

Research has indicated that protein-coding genes serve roles in the physiological mechanism of PCa-induced bone metastasis. Among them, TSPAN18 (23), IFITM3 (24), FN14 (28), FZD8 (32), TBX2 (33) and MAZ (34) directly promote PCa-induced bone metastasis through related molecular pathways. PCa-derived RAGE (30), spondin 2 (45) and FBXO22 (46) are involved in the interaction with bone tissue to promote the differentiation and osteogenic injury of PCa cells. In addition, the adhesion of PCa metastasis to bone is accomplished by RANKL (47), PSCA (50), DDR2 (51), β1 integrin (54) and WISP-1 (56) molecules. PCa cells are regulated by the bone microenvironment after colonizing bone tissue, and the molecules involved in this mechanism mainly include GDF15 (60), RBM3 (35), regucalcin (37) and SIRT5 (38).

Exosomes derived from PCa have been demonstrated to enhance metastasis-associated processes, including the differentiation and proliferation of osteoblasts and osteoclasts (66). Exosomes contain a large number of miRNAs, and abnormal expression of miRNAs leads to abnormal bone remodeling in PCa. Studies have confirmed that miR-375 (67), miR-1-3p/143-3p/145-5p (69), miR-409-3p/-5p (70), miR-210-3p (71), miR-141-3p (74), miR-532-3p (73) and others promote PCa-induced bone metastasis as epigenetic regulatory mechanisms. In addition, studies have found that lncRNAs are involved in the bone metastases process of PCa. Studies have confirmed that PCAT6 (26), NAP1L6 (68), TMPO-AS1 (L) (92), SNHG3 (93), HOXA11-AS (94), PCAT7 (95), KCNQ1OT1 (96), NORAD (97) and NEAT1 (98) exert crucial roles in the bone metastases of PCa.

Currently, the utilization of PSMA PET/CT technology for the detection of PCa has been progressively implemented and has shown promising therapeutic outcomes. Furthermore, PSMA PET/CT offers enhanced sensitivity and specificity in detecting bone metastases in patients with PCa, enabling improved staging, personalized treatment planning and improved monitoring of disease progression (104). In the face of the challenges in the treatment of PCa-induced bone metastasis, the development of novel targeted drugs and the reduction of bone-related events are currently the focus of clinical diagnosis and treatment (120). A study has indicated that PCa cells and bone tissue-related molecules have the potential to be novel targets for the prevention of PCa-related bone metastasis (159). Additionally, clinical trials have confirmed that dinomumab has the ability to decrease bone brittleness and delay the advancement of bone metastases in patients with PCa (124,160). Promising outcomes for patients with bone-metastatic PCa have also been reported in a clinical trial that examined tyrosine kinase inhibitors, such as cabozantinib and dasatinib (127). Therefore, targeted therapy of PCa-related bone metastases has great potential. More basic research is needed to confirm that the identified targets have specific effects on PCa-related bone metastases. The phenomenon of the same target acting on PCa-related bone metastases through different signaling pathways also exists (42,43,60,61), which poses a challenge for targeted therapy. Additionally, the effectiveness and potential adverse reactions of utilizing these targets for the treatment of PCa-induced bone metastasis require validation in additional clinical trials.

Furthermore, the development of resistance to AR inhibitors in metastatic PCa poses a challenge in treatment efficacy. Mechanisms such as AR mutations, alternative splicing and activation of bypass signaling pathways contribute to this resistance, rendering standard therapies less effective (161). Additionally, the tumor microenvironment in the bone can facilitate adaptive changes that promote survival and proliferation of cancer cells despite AR inhibition (44). To overcome these hurdles, novel therapeutic strategies could involve combination therapies targeting not only the AR but also the accompanying signaling pathways and the unique bone microenvironment. These innovative approaches may enhance treatment responses and improve patient outcomes.

In the context of PCa bone metastasis treatment, stem cells offer innovative therapeutic avenues beyond bone differentiation. For instance, targeting the stem cell niche microenvironment could enhance therapeutic strategies, as shown by a study indicating that manipulating this niche can potentially reverse aging-associated changes and improve regenerative outcomes (162). Additionally, the investigation of $CD33^+$ leukemic stem cells highlights the potential for targeted therapies in PCa. Their modulation may provide insights into overcoming resistance mechanisms that hinder current treatment modalities (163). Additionally, insights from cardiac $c\text{-}Kit^+$ progenitor cells have elucidated that stem cell signaling pathways, such as the PI3K and MAPK pathways, serve critical roles in cellular regeneration and may be leveraged to develop novel treatments for PCa (164). Thus, harnessing stem cell properties and their microenvironment can pave the way for innovative approaches in combating PCa bone metastasis.

7. Conclusions

In summary, both coding and non-coding RNAs have effects on the advancement of PCa-related bone metastases, with dual effects of both promotion and inhibition. The identification of specific pathway targets will have an impact on the management of bone metastases in patients with PCa. Furthermore, PSMA, PARP and PD-1 have been employed for the detection and management of bone metastases in patients with PCa. Major changes are expected to occur in the diagnosis and treatment of this disease, as the molecular mechanisms of bone metastases in patients with PCa are gradually understood.

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Authors' contributions

XG and SL were responsible for the conception and execution of this article, and both authors were responsible for the production of pictures and language polishing. Both authors contributed to the manuscript and agreed to contribute to this edition. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD, Wagle NS and Jemal A: Cancer statistics, 2023. CA Cancer J Clin 73: 17-48, 2023.
2. Xia C, Dong X, Li H, Cao M, Sun D, He S, Yang F, Yan X, Zhang S, Li N and Chen W: Cancer statistics in China and United States, 2022: Profiles, trends, and determinants. Chin Med J (Engl) 135: 584-590, 2022.
3. Simmons JK, Hildreth BE III, Supsavhad W, Elshafae SM, Hassan BB, Dirksen WP, Toribio RE and Rosol TJ: Animal models of bone metastasis. Vet Pathol 52: 827-841, 2015.
4. Huang SH, Kao YH, Muller CJF, Joubert E and Chuu CP: Aspalathin-rich green Aspalathus linearis extract suppresses migration and invasion of human castration-resistant prostate cancer cells via inhibition of YAP signaling. Phytomedicine 69: 153210, 2020.
5. Gebrael G, Fortuna GG, Sayegh N, Swami U and Agarwal N: Advances in the treatment of metastatic prostate cancer. Trends Cancer 9: 840-854, 2023.
6. Skotheim RI, Bogaard M, Carm KT, Axcrona U and Axcrona K: Prostate cancer: Molecular aspects, consequences, and opportunities of the multifocal nature. Biochim Biophys Acta Rev Cancer 1879: 189080, 2024.
7. Yu Z, Zou H, Wang H, Li Q and Yu D: Identification of key gene signatures associated with bone metastasis in castration-resistant prostate cancer using co-expression analysis. Front Oncol 10: 571524, 2020.
8. Qu L, Li S, Zhuo Y, Chen J, Qin X and Guo G: Anticancer effect of triterpenes from Ganoderma lucidum in human prostate cancer cells. Oncol Lett 14: 7467-7472, 2017.
9. Morale MG, Tamura RE and Rubio IGS: Metformin and cancer hallmarks: Molecular mechanisms in thyroid, prostate and head and neck cancer models. Biomolecules 12: 357, 2022.
10. Chi JT, Lin PH, Tolstikov V, Oyekunle T, Chen EY, Bussberg V, Greenwood B, Sarangarajan R, Narain NR, Kiebish MA and Freedland SJ: Metabolomic effects of androgen deprivation therapy treatment for prostate cancer. Cancer Med 9: 3691-3702, 2020.
11. Salji M, Hendry J, Patel A, Ahmad I, Nixon C and Leung HY: Peri-prostatic fat volume measurement as a predictive tool for castration resistance in advanced prostate cancer. Eur Urol Focus 4: 858-866, 2018.
12. Yang L, Jin M, Park SJ, Seo SY and Jeong KW: SETD1A promotes proliferation of castration-resistant prostate cancer cells via FOXM1 transcription. Cancers (Basel) 12: 1736, 2020.
13. Boopathi E, Birbe R, Shoyele SA, Den RB and Thangavel C: Bone health management in the continuum of prostate cancer disease. Cancers (Basel) 14: 4305, 2022.
14. Talreja DB: Importance of antiresorptive therapies for patients with bone metastases from solid tumors. Cancer Manag Res 4: 287-297, 2012.
15. Clézardin P, Coleman R, Puppo M, Ottewell P, Bonnelye E, Paycha F, Confavreux CB and Holen I: Bone metastasis: Mechanisms, therapies, and biomarkers. Physiol Rev 101: 797-855, 2021.
16. Sgouros G, Bodei L, McDevitt MR and Nedrow JR: Radiopharmaceutical therapy in cancer: Clinical advances and challenges. Nat Rev Drug Discov 19: 589-608, 2020.
17. Lawal IO, Ndlovu H, Kgatle M, Mokoala KMG and Sathekge MM: Prognostic value of PSMA PET/CT in prostate cancer. Semin Nucl Med 54: 46-59, 2024.
18. Houshmand S, Lawhn-Heath C and Behr S: PSMA PET imaging in the diagnosis and management of prostate cancer. Abdom Radiol (NY) 48: 3610-3623, 2023.
19. Pyka T, Okamoto S, Dahlbender M, Tauber R, Retz M, Heck M, Tamaki N, Schwaiger M, Maurer T and Eiber M: Comparison of bone scintigraphy and (68)Ga-PSMA PET for skeletal staging in prostate cancer. Eur J Nucl Med Mol Imaging 43: 2114-2121, 2016.
20. Harmon SA, Bergvall E, Mena E, Shih JH, Adler S, McKinney Y, Mehralivand S, Citrin DE, Couvillon A, Madan RA, *et al*: A prospective comparison of ^{18}F-sodium fluoride PET/CT and PSMA-Targeted ^{18}F-DCFBC PET/CT in metastatic prostate cancer. J Nucl Med 59: 1665-1671, 2018.
21. Luna A, Vilanova JC and Alcalá Mata L: Total body MRI in early detection of bone metastasis and its indication in comparison to bone scan and other imaging techniques. Arch Esp Urol 68: 371-390, 2015 (In Spanish).
22. Kang J, La Manna F, Bonollo F, Sampson N, Alberts IL, Mingels C, Afshar-Oromieh A, Thalmann GN and Karkampouna S: Tumor microenvironment mechanisms and bone metastatic disease progression of prostate cancer. Cancer Lett 530: 156-169, 2022.
23. Zhou Q, Chen X, Yao K, Zhang Y, He H, Huang H, Chen H, Peng S, Huang M, Cheng L, *et al*: TSPAN18 facilitates bone metastasis of prostate cancer by protecting STIM1 from TRIM32-mediated ubiquitination. J Exp Clin Cancer Res 42: 195, 2023.
24. Liu X, Chen L, Fan Y, Hong Y, Yang X, Li Y, Lu J, Lv J, Pan X, Qu F, *et al*: IFITM3 promotes bone metastasis of prostate cancer cells by mediating activation of the TGF-β signaling pathway. Cell Death Dis 10: 517, 2019.
25. Abramovic I, Ulamec M, Katusic Bojanac A, Bulic-Jakus F, Jezek D and Sincic N: miRNA in prostate cancer: Challenges toward translation. Epigenomics 12: 543-558, 2020.
26. Lang C, Yin C, Lin K, Li Y, Yang Q, Wu Z, Du H, Ren D, Dai Y and Peng X: m^{6}A modification of lncRNA PCAT6 promotes bone metastasis in prostate cancer through IGF2BP2-mediated IGF1R mRNA stabilization. Clin Transl Med 11: e426, 2021.
27. Li FX, Liu JJ, Xu F, Lin X, Zhong JY, Wu F and Yuan LQ: Role of tumor-derived exosomes in bone metastasis. Oncol Lett 18: 3935-3945, 2019.
28. Yin J, Liu YN, Tillman H, Barrett B, Hewitt S, Ylaya K, Fang L, Lake R, Corey E, Morrissey C, *et al*: AR-regulated TWEAK-FN14 pathway promotes prostate cancer bone metastasis. Cancer Res 74: 4306-4317, 2014.
29. Huang H, Weng H and Chen J: m^{6}A modification in coding and non-coding RNAs: Roles and therapeutic implications in cancer. Cancer Cell 37: 270-288, 2020.
30. Kolonin MG, Sergeeva A, Staquicini DI, Smith TL, Tarleton CA, Molldrem JJ, Sidman RL, Marchiò S, Pasqualini R and Arap W: Interaction between tumor cell surface receptor RAGE and proteinase 3 mediates prostate cancer metastasis to bone. Cancer Res 77: 3144-3150, 2017.
31. Park M, Cho YJ, Kim B, Ko YJ, Jang Y, Moon YH, Hyun H and Lim W: RANKL immunisation inhibits prostate cancer metastasis by modulating EMT through a RANKL-dependent pathway. Sci Rep 11: 12186, 2021.
32. Li Q, Ye L, Zhang X, Wang M, Lin C, Huang S, Guo W, Lai Y, Du H, Li J, *et al*: FZD8, a target of p53, promotes bone metastasis in prostate cancer by activating canonical Wnt/β-catenin signaling. Cancer Lett 402: 166-176, 2017.
33. Nandana S, Tripathi M, Duan P, Chu CY, Mishra R, Liu C, Jin R, Yamashita H, Zayzafoon M, Bhowmick NA, *et al*: Bone metastasis of prostate cancer can be therapeutically targeted at the TBX2-WNT signaling axis. Cancer Res 77: 1331-1344, 2017.

34. Yang Q, Lang C, Wu Z, Dai Y, He S, Guo W, Huang S, Du H, Ren D and Peng X: MAZ promotes prostate cancer bone metastasis through transcriptionally activating the KRas-dependent RalGEFs pathway. J Exp Clin Cancer Res 38: 391, 2019.
35. Zhang S, Lv C, Niu Y, Li C, Li X, Shang Y, Zhang Y, Zhang Y, Zhang Y and Zeng Y: RBM3 suppresses stemness remodeling of prostate cancer in bone microenvironment by modulating N6-methyladenosine on CTNNB1 mRNA. Cell Death Dis 14: 91, 2023.
36. Yamaguchi M, Murata T and Ramos JW: Extracellular regucalcin suppresses the growth, migration, invasion, and adhesion of metastatic human prostate cancer cells. Oncology 100: 399-412, 2022.
37. Yamaguchi M, Murata T and Ramos JW: Overexpression of regucalcin blocks the migration, invasion, and bone metastatic activity of human prostate cancer cells: Crosstalk between cancer cells and bone cells. Prostate 82: 1025-1039, 2022.
38. Lagunas-Rangel FA: Role of SIRT5 in cancer. Friend or Foe? Biochimie 209: 131-141, 2023.
39. Wang X, Li Z and Sun Y: T-box transcription factor 2 mediates antitumor immune response in cutaneous squamous cell carcinoma by regulating the expression of programmed death ligand 1. Skin Res Technol 29: e13254, 2023.
40. Trivedi T, Pagnotti GM, Guise TA and Mohammad KS: The role of TGF-β in bone metastases. Biomolecules 11: 1643, 2021.
41. Gerratana L, Davis AA, Polano M, Zhang Q, Shah AN, Lin C, Basile D, Toffoli G, Wehbe F, Puglisi F, *et al*: Understanding the organ tropism of metastatic breast cancer through the combination of liquid biopsy tools. Eur J Cancer 143: 147-157, 2021.
42. Yonezawa I, Waki M, Tamura Y, Onoda R, Narushima M, Ishizuka T and Tajima S: Gemcitabine-based regimen for primary ovarian angiosarcoma with MYC amplification. Curr Oncol 21: e782-e789, 2014.
43. Stopsack KH, Nandakumar S, Wibmer AG, Haywood S, Weg ES, Barnett ES, Kim CJ, Carbone EA, Vasselman SE, Nguyen B, *et al*: Oncogenic genomic alterations, clinical phenotypes, and outcomes in metastatic castration-sensitive prostate cancer. Clin Cancer Res 26: 3230-3238, 2020.
44. Archer Goode E, Wang N and Munkley J: Prostate cancer bone metastases biology and clinical management (Review). Oncol Lett 25: 163, 2023.
45. Wang H, Zhang M, Lu W and Yuan C: Prostate cancer cell-derived spondin 2 boosts osteogenic factor levels in osteoblasts via the PI3K/AKT/mTOR pathway. Oncol Rep 49: 23, 2023.
46. Zhang Y, Li W, Guo S, Wu Z, Zhang L, Liu Y, Li X, Guo X, Cao J, Yang C and Wang Z: FBXO22 mediates the NGF/TRKA signaling pathway in bone metastases in prostate cancer. Am J Pathol 193: 1248-1266, 2023.
47. Ziaee S and Chung LWK: Induction of integrin α2 in a highly bone metastatic human prostate cancer cell line: Roles of RANKL and AR under three-dimensional suspension culture. Mol Cancer 13: 208, 2014.
48. Ye XC, Choueiri M, Tu SM and Lin SH: Biology and clinical management of prostate cancer bone metastasis. Front Biosci 12: 3273-3286, 2007.
49. Nayerpour Dizaj T, Doustmihan A, Sadeghzadeh Oskouei B, Akbari M, Jaymand M, Mazloomi M and Jahanban-Esfahlan R: Significance of PSCA as a novel prognostic marker and therapeutic target for cancer. Cancer Cell Int 24: 135, 2024.
50. Zhao Z, Li E, Luo L, Zhao S, Liu L, Wang J, Kang R and Luo J: A PSCA/PGRN-NF-κB-integrin-α4 axis promotes prostate cancer cell adhesion to bone marrow endothelium and enhances metastatic potential. Mol Cancer Res 18: 501-513, 2020.
51. Azemikhah M, Ashtiani HA, Aghaei M and Rastegar H: Evaluation of discoidin domain receptor-2 (DDR2) expression level in normal, benign, and malignant human prostate tissues. Res Pharm Sci 10: 356-363, 2015.
52. Yan Z, Jin S, Wei Z, Huilian H, Zhanhai Y, Yue T, Juan L, Jing L, Libo Y and Xu L: Discoidin domain receptor 2 facilitates prostate cancer bone metastasis via regulating parathyroid hormone-related protein. Biochim Biophys Acta 1842: 1350-1363, 2014.
53. Calderwood DA, Campbell ID and Critchley DR: Talins and kindlins: Partners in integrin-mediated adhesion. Nat Rev Mol Cell Biol 14: 503-517, 2013.
54. Jin JK, Tien PC, Cheng CJ, Song JH, Huang C, Lin SH and Gallick GE: Talin1 phosphorylation activates β1 integrins: A novel mechanism to promote prostate cancer bone metastasis. Oncogene 34: 1811-1821, 2015.
55. Holbourn KP, Acharya KR and Perbal B: The CCN family of proteins: Structure-function relationships. Trends Biochem Sci 33: 461-473, 2008.
56. Tai HC, Chang AC, Yu HJ, Huang CY, Tsai YC, Lai YW, Sun HL, Tang CH and Wang SW: Osteoblast-derived WNT-induced secreted protein 1 increases VCAM-1 expression and enhances prostate cancer metastasis by down-regulating miR-126. Oncotarget 5: 7589-7598, 2014.
57. Chang AC, Chen PC, Lin YF, Su CM, Liu JF, Lin TH, Chuang SM and Tang CH: Osteoblast-secreted WISP-1 promotes adherence of prostate cancer cells to bone via the VCAM-1/integrin α4β1 system. Cancer Lett 426: 47-56, 2018.
58. Yao L and Zhang X: Interaction between prostate cancer stem cells and bone microenvironment regulates prostate cancer bone metastasis and treatment resistance. J Cancer 13: 2757-2767, 2022.
59. Choi SY, Jeon JM, Na AY, Kwon OK, Bang IH, Ha YS, Bae EJ, Park BH, Lee EH, Kwon TG, *et al*: SIRT5 directly inhibits the PI3K/AKT pathway in prostate cancer cell lines. Cancer Genomics Proteomics 19: 50-59, 2022.
60. Siddiqui JA, Seshacharyulu P, Muniyan S, Pothuraju R, Khan P, Vengoji R, Chaudhary S, Maurya SK, Lele SM, Jain M, *et al*: GDF15 promotes prostate cancer bone metastasis and colonization through osteoblastic CCL2 and RANKL activation. Bone Res 10: 6, 2022.
61. Toden S, Zumwalt TJ and Goel A: Non-coding RNAs and potential therapeutic targeting in cancer. Biochim Biophys Acta Rev Cancer 1875: 188491, 2021.
62. Loganathan T and Doss C GP: Non-coding RNAs in human health and disease: Potential function as biomarkers and therapeutic targets. Funct Integr Genomics 23: 33, 2023.
63. Ma L, Bajic VB and Zhang Z: On the classification of long non-coding RNAs. RNA Biol 10: 925-933, 2013.
64. Bhan A, Soleimani M and Mandal SS: Long noncoding RNA and cancer: A new paradigm. Cancer Res 77: 3965-3981, 2017.
65. Wang J, Yue BL, Huang YZ, Lan XY, Liu WJ and Chen H: Exosomal RNAs: Novel potential biomarkers for diseases-a review. Int J Mol Sci 23: 2461, 2022.
66. Prigol AN, Rode MP, da Luz Efe F, Saleh NA and Creczynski-Pasa TB: The bone microenvironment soil in prostate cancer metastasis: An miRNA approach. Cancers (Basel) 15: 4027, 2023.
67. Liu Y, Yang C, Chen S, Liu W, Liang J, He S and Hui J: Cancer-derived exosomal miR-375 targets DIP2C and promotes osteoblastic metastasis and prostate cancer progression by regulating the Wnt signaling pathway. Cancer Gene Ther 30: 437-449, 2023.
68. Zheng Y, Qi F, Li L, Yu B, Cheng Y, Ge M, Qin C and Li X: LncNAP1L6 activates MMP pathway by stabilizing the m6A-modified NAP1L2 to promote malignant progression in prostate cancer. Cancer Gene Ther 30: 209-218, 2023.
69. Guo H, Zhao J, Li X, Sun F, Qin Y, Yang X, Xiong X, Yin Q, Wang X, Gao L, *et al*: Identification of miR-1-3p, miR-143-3p and miR-145-5p association with bone metastasis of Gleason 3+4 prostate cancer and involvement of LASP1 regulation. Mol Cell Probes 68: 101901, 2023.
70. Josson S, Gururajan M, Hu P, Shao C, Chu GY, Zhau HE, Liu C, Lao K, Lu CL, Lu YT, *et al*: miR-409-3p/-5p promotes tumorigenesis, epithelial-to-mesenchymal transition, and bone metastasis of human prostate cancer. Clin Cancer Res 20: 4636-4646, 2014.
71. Dai Y, Ren D, Yang Q, Cui Y, Guo W, Lai Y, Du H, Lin C, Li J, Song L and Peng X: The TGF-β signalling negative regulator PICK1 represses prostate cancer metastasis to bone. Br J Cancer 117: 685-694, 2017.
72. Ye Y, Li SL, Ma YY, Diao YJ, Yang L, Su MQ, Li Z, Ji Y, Wang J, Lei L, *et al*: Exosomal miR-141-3p regulates osteoblast activity to promote the osteoblastic metastasis of prostate cancer. Oncotarget 8: 94834-94849, 2017.
73. Wa Q, Zou C, Lin Z, Huang S, Peng X, Yang C, Ren D, Xu D, Guo Y, Liao Z, *et al*: Ectopic expression of miR-532-3p suppresses bone metastasis of prostate cancer cells via inactivating NF-κB signaling. Mol Ther Oncolytics 17: 267-277, 2020.
74. Ren D, Yang Q, Dai Y, Guo W, Du H, Song L and Peng X: Oncogenic miR-210-3p promotes prostate cancer cell EMT and bone metastasis via NF-κB signaling pathway. Mol Cancer 16: 117, 2017.
75. Chen Q, Zhang H, Zhang J, Shen L, Yang J, Wang Y, Ma J and Zhuan B: miR-210-3p promotes lung cancer development and progression by modulating USF1 and PCGF3. Onco Targets Ther 14: 3687-3700, 2021.

76. Tuo X, Zhou Y, Yang X, Ma S, Liu D, Zhang X, Hou H, Wang R, Li X and Zhao L: miR-532-3p suppresses proliferation and invasion of ovarian cancer cells via GPNMB/HIF-1α/HK2 axis. Pathol Res Pract 237: 154032, 2022.
77. Luo B, Yuan Y, Zhu Y, Liang S, Dong R, Hou J, Li P, Xing Y, Lu Z, Lo R and Kuang GM: microRNA-145-5p inhibits prostate cancer bone metastatic by modulating the epithelial-mesenchymal transition. Front Oncol 12: 988794, 2022.
78. Chang YS, Chen WY, Yin JJ, Sheppard-Tillman H, Huang J and Liu YN: EGF receptor promotes prostate cancer bone metastasis by downregulating miR-1 and activating TWIST1. Cancer Res 75: 3077-3086, 2015.
79. Fu Q, Liu X, Liu Y, Yang J, Lv G and Dong S: MicroRNA-335 and -543 suppress bone metastasis in prostate cancer via targeting endothelial nitric oxide synthase. Int J Mol Med 36: 1417-1425, 2015.
80. Colden M, Dar AA, Saini S, Dahiya PV, Shahryari V, Yamamura S, Tanaka Y, Stein G, Dahiya R and Majid S: MicroRNA-466 inhibits tumor growth and bone metastasis in prostate cancer by direct regulation of osteogenic transcription factor RUNX2. Cell Death Dis 8: e2572, 2017.
81. Huang S, Wa Q, Pan J, Peng X, Ren D, Huang Y, Chen X and Tang Y: Downregulation of miR-141-3p promotes bone metastasis via activating NF-κB signaling in prostate cancer. J Exp Clin Cancer Res 36: 173, 2017.
82. Huang S, Wa Q, Pan J, Peng X, Ren D, Li Q, Dai Y, Yang Q, Huang Y, Zhang X, *et al*: Transcriptional downregulation of miR-133b by REST promotes prostate cancer metastasis to bone via activating TGF-β signaling. Cell Death Dis 9: 779, 2018.
83. Huang S, Zou C, Tang Y, Wa Q, Peng X, Chen X, Yang C, Ren D, Huang Y, Liao Z, *et al*: miR-582-3p and miR-582-5p suppress prostate cancer metastasis to bone by repressing TGF-β signaling. Mol Ther Nucleic Acids 16: 91-104, 2019.
84. Wa Q, Huang S, Pan J, Tang Y, He S, Fu X, Peng X, Chen X, Yang C, Ren D, *et al*: miR-204-5p represses bone metastasis via inactivating NF-κB signaling in prostate cancer. Mol Ther Nucleic Acids 18: 567-579, 2019.
85. Wa Q, Li L, Lin H, Peng X, Ren D, Huang Y, He P and Huang S: Downregulation of miR-19a-3p promotes invasion, migration and bone metastasis via activating TGF-β signaling in prostate cancer. Oncol Rep 39: 81-90, 2018.
86. Qu L, Li Z and Liu P: mir-204-5p Acts as a tumor suppressor by targeting DNM2 in osteosarcoma cells. J Healthc Eng 2022: 8944588, 2022.
87. Sun R, Wei T, Ding D, Zhang J, Chen S, He HH, Wang L and Huang H: CYCLIN K down-regulation induces androgen receptor gene intronic polyadenylation, variant expression and PARP inhibitor vulnerability in castration-resistant prostate cancer. Proc Natl Acad Sci USA 119: e2205509119, 2022.
88. Yang S, Chen B, Zhang B, Li C, Qiu Y, Yang H and Huang Z: miR-204-5p promotes apoptosis and inhibits migration of gastric cancer cells by targeting HER-2. Mol Med Rep 22: 2645-2654, 2020.
89. Peng L, Li P and Peng Z: miR-141-3p enhanced radiosensitivity of CRC cells. Comb Chem High Throughput Screen 27: 118-126, 2024.
90. Liu Y, Fu W, Yin F, Xia L, Zhang Y, Wang B, Li T, Zhang T, Cheng L, Wei Y and Gao B: miR-141-3p suppresses development of clear cell renal cell carcinoma by regulating NEK6. Anticancer Drugs 33: e125-e133, 2022.
91. Ferraz RS, Cavalcante JVF, Magalhães L, Ribeiro-Dos-Santos Â and Dalmolin RJS: Revealing metastatic castration-resistant prostate cancer master regulator through lncRNAs-centered regulatory network. Cancer Med 12: 19279-19290, 2023.
92. Wang M, Yin C, Wu Z, Wang X, Lin Q, Jiang X, Du H, Lang C, Peng X and Dai Y: The long transcript of lncRNA TMPO-AS1 promotes bone metastases of prostate cancer by regulating the CSNK2A1/DDX3X complex in Wnt/β-catenin signaling. Cell Death Discov 9: 287, 2023.
93. Xi X, Hu Z, Wu Q, Hu K, Cao Z, Zhou J, Liao J, Zhang Z, Hu Y, Zhong X and Bao Y: High expression of small nucleolar RNA host gene 3 predicts poor prognosis and promotes bone metastasis in prostate cancer by activating transforming growth factor-beta signaling. Bioengineered 13: 1895-1907, 2022.
94. Misawa A, Kondo Y, Takei H and Takizawa T: Long noncoding RNA HOXA11-AS and transcription factor HOXB13 modulate the expression of bone metastasis-related genes in prostate cancer. Genes (Basel) 12: 182, 2021.
95. Lang C, Dai Y, Wu Z, Yang Q, He S, Zhang X, Guo W, Lai Y, Du H, Wang H, *et al*: SMAD3/SP1 complex-mediated constitutive active loop between lncRNA PCAT7 and TGF-β signaling promotes prostate cancer bone metastasis. Mol Oncol 14: 808-828, 2020.
96. Hao H, Chen H, Xie L, Liu H and Wang D: LncRNA KCNQ1OT1 promotes proliferation, invasion and metastasis of prostate cancer by regulating miR-211-5p/CHI3L1 pathway. Onco Targets Ther 14: 1659-1671, 2021.
97. Hu CY, Chen J, Qin XH, You P, Ma J, Zhang J, Zhang H and Xu JD: Long non-coding RNA NORAD promotes the prostate cancer cell extracellular vesicle release via microRNA-541-3p-regulated PKM2 to induce bone metastasis of prostate cancer. J Exp Clin Cancer Res 40: 98, 2021.
98. Mo C, Huang B, Zhuang J, Jiang S, Guo S and Mao X: LncRNA nuclear-enriched abundant transcript 1 shuttled by prostate cancer cells-secreted exosomes initiates osteoblastic phenotypes in the bone metastatic microenvironment via miR-205-5p/runt-related transcription factor 2/splicing factor proline- and glutamine-rich/polypyrimidine tract-binding protein 2 axis. Clin Transl Med 11: e493, 2021.
99. Ma Q, Qi X, Lin X, Li L, Chen L and Hu W: LncRNA SNHG3 promotes cell proliferation and invasion through the miR-384/hepatoma-derived growth factor axis in breast cancer. Hum Cell 33: 232-242, 2020.
100. Zheng S, Jiang F, Ge D, Tang J, Chen H, Yang J, Yao Y, Yan J, Qiu J, Yin Z, *et al*: LncRNA SNHG3/miRNA-151a-3p/RAB22A axis regulates invasion and migration of osteosarcoma. Biomed Pharmacother 112: 108695, 2019.
101. Xuan Y and Wang Y: Long non-coding RNA SNHG3 promotes progression of gastric cancer by regulating neighboring MED18 gene methylation. Cell Death Dis 10: 694, 2019.
102. Fendler WP, Eiber M, Beheshti M, Bomanji J, Calais J, Ceci F, Cho SY, Fanti S, Giesel FL, Goffin K, *et al*: PSMA PET/CT: Joint EANM procedure guideline/SNMMI procedure standard for prostate cancer imaging 2.0. Eur J Nucl Med Mol Imaging 50: 1466-1486, 2023.
103. Eiber M, Herrmann K, Calais J, Hadaschik B, Giesel FL, Hartenbach M, Hope T, Reiter R, Maurer T, Weber WA and Fendler WP: Prostate cancer molecular imaging standardized evaluation (PROMISE): Proposed miTNM classification for the interpretation of PSMA-ligand PET/CT. J Nucl Med 59: 469-478, 2018.
104. Regula N, Kostaras V, Johansson S, Trampal C, Lindström E, Lubberink M, Iyer V, Velikyan I and Sörensen J: Comparison of ^{68}Ga-PSMA PET/CT with fluoride PET/CT for detection of bone metastatic disease in prostate cancer. Eur J Hybrid Imaging 6: 5, 2022.
105. Brenner AI, Koshy J, Morey J, Lin C and DiPoce J: The bone scan. Semin Nucl Med 42: 11-26, 2012.
106. Even-Sapir E, Metser U, Mishani E, Lievshitz G, Lerman H and Leibovitch I: The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. J Nucl Med 47: 287-297, 2006.
107. Calais J, Ceci F, Eiber M, Hope TA, Hofman MS, Rischpler C, Bach-Gansmo T, Nanni C, Savir-Baruch B, Elashoff D, *et al*: ^{18}F-fluciclovine PET-CT and ^{68}Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: A prospective, single-centre, single-arm, comparative imaging trial. Lancet Oncol 20: 1286-1294, 2019.
108. van Boxtel W, Lütje S, van Engen-van Grunsven ICH, Verhaegh GW, Schalken JA, Jonker MA, Nagarajah J, Gotthardt M and van Herpen CML: ^{68}Ga-PSMA-HBED-CC PET/CT imaging for adenoid cystic carcinoma and salivary duct carcinoma: A phase 2 imaging study. Theranostics 10: 2273-2283, 2020.
109. Sonni I, Felker ER, Lenis AT, Sisk AE, Bahri S, Allen-Auerbach M, Armstrong WR, Suvannarerg V, Tubtawee T, Grogan T, *et al*: Head-to-head comparison of ^{68}Ga-PSMA-11 PET/CT and mpMRI with a histopathology gold standard in the detection, intraprostatic localization, and determination of local extension of primary prostate cancer: Results from a prospective single-center imaging trial. J Nucl Med 63: 847-854, 2022.
110. Zhou J, Gou Z, Wu R, Yuan Y, Yu G and Zhao Y: Comparison of PSMA-PET/CT, choline-PET/CT, NaF-PET/CT, MRI, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: A systematic review and meta-analysis. Skeletal Radiol 48: 1915-1924, 2019.
111. Zhou J, Wu R, Wang W, Zhao Y and Liu X: ^{68}Ga-PSMA PET/CT for the detection of bone metastases in prostate cancer: A systematic review of the published literature. Clin Physiol Funct Imaging: Oct 29, 2017 (Epub ahead of print).

112. Coleman RE, Croucher PI, Padhani AR, Clézardin P, Chow E, Fallon M, Guise T, Colangeli S, Capanna R and Costa L: Bone metastases. Nat Rev Dis Primers 6: 83, 2020.
113. Urabe F, Kosaka N, Yamamoto Y, Ito K, Otsuka K, Soekmadji C, Egawa S, Kimura T and Ochiya T: Metastatic prostate cancer-derived extracellular vesicles facilitate osteoclastogenesis by transferring the CDCP1 protein. J Extracell Vesicles 12: e12312, 2023.
114. Hu C, Chen Q, Wu T, Du X, Dong Y, Peng Z, Xue W, Sunkara V, Cho YK and Dong L: The role of extracellular vesicles in the treatment of prostate cancer. Small 20: e2311071, 2024.
115. Wang Y, Fang YX, Dong B, Du X, Wang J, Wang X, Gao WQ and Xue W: Discovery of extracellular vesicles derived miR-181a-5p in patient's serum as an indicator for bone-metastatic prostate cancer. Theranostics 11: 878-892, 2021.
116. Yu L, Sui B, Fan W, Lei L, Zhou L, Yang L, Diao Y, Zhang Y, Li Z, Liu J and Hao X: Exosomes derived from osteogenic tumor activate osteoclast differentiation and concurrently inhibit osteogenesis by transferring COL1A1-targeting miRNA-92a-1-5p. J Extracell Vesicles 10: e12056, 2021.
117. Wang J, Du X, Wang X, Xiao H, Jing N, Xue W, Dong B, Gao WQ and Fang YX: Tumor-derived miR-378a-3p-containing extracellular vesicles promote osteolysis by activating the Dyrk1a/Nfatc1/Angptl2 axis for bone metastasis. Cancer Lett 526: 76-90, 2022.
118. Zeng F, Zhao C, Wang R, Ren L, Qiu H, Zou Z, Ding H, Sun Z, Li J and Dong S: Antagonizing exosomal miR-18a-5p derived from prostate cancer cells ameliorates metastasis-induced osteoblastic lesions by targeting Hist1h2bc and activating Wnt/β-catenin pathway. Genes Dis 10: 1626-1640, 2022.
119. Baldessari C, Pipitone S, Molinaro E, Cerma K, Fanelli M, Nasso C, Oltrecolli M, Pirola M, D'Agostino E, Pugliese G, *et al*: Bone metastases and health in prostate cancer: From pathophysiology to clinical implications. Cancers (Basel) 15: 1518, 2023.
120. Schwartz GG: Prostate cancer, serum parathyroid hormone, and the progression of skeletal metastases. Cancer Epidemiol Biomarkers Prev 17: 478-483, 2008.
121. Yuan S, Hoggard NK, Kantake N, Hildreth BE III and Rosol TJ: Effects of dickkopf-1 (DKK-1) on prostate cancer growth and bone metastasis. Cells 12: 2695, 2023.
122. Zhang B, Li Y, Wu Q, Xie L, Barwick B, Fu C, Li X, Wu D, Xia S, Chen J, *et al*: Acetylation of KLF5 maintains EMT and tumorigenicity to cause chemoresistant bone metastasis in prostate cancer. Nat Commun 12: 1714, 2021.
123. Gomez-Veiga F, Ponce-Reixa J, Martinez-Breijo S, Planas J and Morote J: Advances in prevention and treatment of bone metastases in prostate cancer. Role of RANK/RANKL inhibition. Actas Urol Esp 37: 292-304, 2013 (In English, Spanish).
124. Mizuta K, Oshiro H, Katsuki R, Tsuha Y, Aoki Y, Tome Y and Nishida K: Denosumab administration for bone metastases from solid tumors: A retrospective cross-sectional study. BMC Cancer 23: 999, 2023.
125. Agarwal N, McGregor B, Maughan BL, Dorff TB, Kelly W, Fang B, McKay RR, Singh P, Pagliaro L, Dreicer R, *et al*: Cabozantinib in combination with atezolizumab in patients with metastatic castration-resistant prostate cancer: Results from an expansion cohort of a multicentre, open-label, phase 1b trial (COSMIC-021). Lancet Oncol 23: 899-909, 2022.
126. Yu EY, Wilding G, Posadas E, Gross M, Culine S, Massard C, Morris MJ, Hudes G, Calabrò F, Cheng S, *et al*: Phase II study of dasatinib in patients with metastatic castration-resistant prostate cancer. Clin Cancer Res 15: 7421-7428, 2009.
127. Qiao L, Liang Y, Li N, Hu X, Luo D, Gu J, Lu Y and Zheng Q: Endothelin-A receptor antagonists in prostate cancer treatment-a meta-analysis. Int J Clin Exp Med 8: 3465-3473, 2015.
128. Lee YT, Tan YJ and Oon CE: Molecular targeted therapy: Treating cancer with specificity. Eur J Pharmacol 834: 188-196, 2018.
129. Reichert ZR, Urrutia J and Alumkal JJ: Microsatellite Instability as an emerging biomarker for checkpoint inhibitor response in advanced prostate cancer. JAMA Oncology 5: 478-479, 2019.
130. Mitsogiannis I, Tzelves L, Dellis A, Issa H, Papatsoris A and Moussa M: Prostate cancer immunotherapy. Expert Opin Biol Ther 22: 577-590, 2022.
131. Wu YM, Cieślik M, Lonigro RJ, Vats P, Reimers MA, Cao X, Ning Y, Wang L, Kunju LP, de Sarkar N, *et al*: Inactivation of CDK12 delineates a distinct immunogenic class of advanced prostate cancer. Cell 173: 1770-1782.e14, 2018.
132. Bochum S, Berger S and Martens UM: Olaparib. Recent Results Cancer Res 211: 217-233, 2018.
133. Risdon EN, Chau CH, Price DK, Sartor O and Figg WD: PARP inhibitors and prostate cancer: To infinity and beyond BRCA. Oncologist 26: e115-e129, 2021.
134. Chen A: PARP inhibitors: Its role in treatment of cancer. Chin J Cancer 30: 463-471, 2011.
135. Stamatakos PV, Fragkoulis C, Leventi A, Gklinos K, Kontolatis N, Papatsoris A and Dellis A: PSMA-based therapeutics for prostate cancer. Expert Opin Pharmacother 25: 1405-1419, 2024.
136. Combes AD, Palma CA, Calopedos R, Wen L, Woo H, Fulham M and Leslie S: PSMA PET-CT in the diagnosis and staging of prostate cancer. Diagnostics (Basel) 12: 2594, 2022.
137. Sun M, Niaz MO, Nelson A, Skafida M and Niaz MJ: Review of 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer. Cureus 12: e8921, 2020.
138. Narayan V, Barber-Rotenberg JS, Jung IY, Lacey SF, Rech AJ, Davis MM, Hwang WT, Lal P, Carpenter EL, Maude SL, *et al*: PSMA-targeting TGFβ-insensitive armored CAR T cells in metastatic castration-resistant prostate cancer: A phase 1 trial. Nat Med 28: 724-734, 2022.
139. Almuradova E, Seyyar M, Arak H, Tamer F, Kefeli U, Koca S, Sen E, Telli TA, Karatas F, Gokmen I, *et al*: The real-world outcomes of Lutetium-177 PSMA-617 radioligand therapy in metastatic castration-resistant prostate cancer: Turkish oncology group multicenter study. Int J Cancer 154: 692-700, 2024.
140. Maharaj M, Heslop L, Govender T, Korowlay N, Singh A, Choudhary P and Sathekge M: The outcome and safety of re-challenge Lutetium-177 PSMA (^{177}Lu-PSMA) therapy with low-dose docetaxel as a radiosensitizer-a promising combination in metastatic castrate-resistant prostate cancer (mCRPC): A case report. Nucl Med Mol Imaging 55: 136-140, 2021.
141. Flegar L, Thoduka SG, Librizzi D, Luster M, Zacharis A, Heers H, Eisenmenger N, Ahmadzadehfar H, Eiber M, Weber W, *et al*: Adoption of Lutetium-^{177} PSMA radioligand therapy for metastatic castration resistant prostate cancer: A total population analysis in Germany from 2016 to 2020. Eur J Nucl Med Mol Imaging 50: 2188-2195, 2023.
142. Khreish F, Ghazal Z, Marlowe RJ, Rosar F, Sabet A, Maus S, Linxweiler J, Bartholomä M and Ezziddin S: 177 Lu-PSMA-617 radioligand therapy of metastatic castration-resistant prostate cancer: Initial 254-patient results from a prospective registry (REALITY study). Eur J Nucl Med Mol Imaging 49: 1075-1085, 2022.
143. Zarrabi KK, Narayan V, Mille PJ, Zibelman MR, Miron B, Bashir B and Kelly WK: Bispecific PSMA antibodies and CAR-T in metastatic castration-resistant prostate cancer. Ther Adv Urol 15: 17562872231182219, 2023.
144. Lund ME, Howard CB, Thurecht KJ, Campbell DH, Mahler SM and Walsh BJ: A bispecific T cell engager targeting Glypican-1 redirects T cell cytolytic activity to kill prostate cancer cells. BMC Cancer 20: 1214, 2020.
145. Yamamoto K, Trad A, Baumgart A, Hüske L, Lorenzen I, Chalaris A, Grötzinger J, Dechow T, Scheller J and Rose-John S: A novel bispecific single-chain antibody for ADAM17 and CD3 induces T-cell-mediated lysis of prostate cancer cells. Biochem J 445: 135-144, 2012.
146. Nyquist MD, Corella A, Coleman I, De Sarkar N, Kaipainen A, Ha G, Gulati R, Ang L, Chatterjee P, Lucas J, *et al*: Combined TP53 and RB1 loss promotes prostate cancer resistance to a spectrum of therapeutics and confers vulnerability to replication stress. Cell Rep 31: 107669, 2020.
147. Patel SA: Managing the unmanageable: Evidence-driven approaches to real-world patient prototypes of TP53-mutant myelodysplastic neoplasms and acute myeloid leukemia. Leukemia: Sep 30, 2024 (Epub ahead of print).
148. Lee YC, Lee YL and Li CY: BRCA genes and related cancers: A meta-analysis from epidemiological cohort studies. Medicina (Kaunas) 57: 905, 2021.
149. Sweeney C, Bracarda S, Sternberg CN, Chi KN, Olmos D, Sandhu S, Massard C, Matsubara N, Alekseev B, Parnis F, *et al*: Ipatasertib plus abiraterone and prednisolone in metastatic castration-resistant prostate cancer (IPATential150): A multicentre, randomised, double-blind, phase 3 trial. Lancet 398: 131-142, 2021.
150. Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, Milecki P, Shore N, Rader M, Wang H, *et al*: Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomised, double-blind study. Lancet 377: 813-822, 2011.

151. Shenderov E, Boudadi K, Fu W, Wang H, Sullivan R, Jordan A, Dowling D, Harb R, Schonhoft J, Jendrisak A, *et al*: Nivolumab plus ipilimumab, with or without enzalutamide, in AR-V7-expressing metastatic castration-resistant prostate cancer: A phase-2 nonrandomized clinical trial. Prostate 81: 326-338, 2021.
152. Graff JN, Beer TM, Alumkal JJ, Slottke RE, Redmond WL, Thomas GV, Thompson RF, Wood MA, Koguchi Y, Chen Y, *et al*: A phase II single-arm study of pembrolizumab with enzalutamide in men with metastatic castration-resistant prostate cancer progressing on enzalutamide alone. J Immunother Cancer 8: e000642, 2020.
153. McNeel DG, Eickhoff JC, Wargowski E, Johnson LE, Kyriakopoulos CE, Emamekhoo H, Lang JM, Brennan MJ and Liu G: Phase 2 trial of T-cell activation using MVI-816 and pembrolizumab in patients with metastatic, castration-resistant prostate cancer (mCRPC). J Immunother Cancer 10: e004198, 2022.
154. Xia QD, Zhang SH, Zeng N, Lu YC, Qin BL and Wang SG: Novel androgen receptor inhibitors for metastatic hormone-sensitive prostate cancer: Current application and future perspectives. Biomed Pharmacother 168: 115806, 2023.
155. Shah H and Vaishampayan U: Therapy of advanced prostate cancer: Targeting the androgen receptor axis in earlier lines of treatment. Target Oncol 13: 679-689, 2018.
156. Zhang Y, Ming A, Wang J, Chen W and Fang Z: PROTACs targeting androgen receptor signaling: Potential therapeutic agents for castration-resistant prostate cancer. Pharmacol Res 205: 107234, 2024.
157. Petrylak DP, Vaishampayan UN, Patel KR, Higano CS, Albany C, Dawson NA, Mehlhaff BA, Quinn DI, Nordquist LT, Wagner VJ, *et al*: A randomized phase IIa study of quantified bone scan response in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with radium-223 dichloride alone or in combination with abiraterone acetate/prednisone or enzalutamide. ESMO Open 6: 100082, 2021.
158. Manna F, Karkampouna S, Zoni E, De Menna M, Hensel J, Thalmann GN and Kruithof-de Julio M: Metastases in prostate cancer. Cold Spring Harb Perspect Med 9: a033688, 2019.
159. Zhang X: Interactions between cancer cells and bone microenvironment promote bone metastasis in prostate cancer. Cancer Commun (Lond) 39: 76, 2019.
160. Lu J, Hu D, Zhang Y, Ma C, Shen L and Shuai B: Current comprehensive understanding of denosumab (the RANKL neutralizing antibody) in the treatment of bone metastasis of malignant tumors, including pharmacological mechanism and clinical trials. Front Oncol 13: 1133828, 2023.
161. Shiota M, Akamatsu S, Tsukahara S, Nagakawa S, Matsumoto T and Eto M: Androgen receptor mutations for precision medicine in prostate cancer. Endocr Relat Cancer 29: R143-R155, 2022.
162. Farahzadi R, Valipour B, Montazersaheb S and Fathi E: Targeting the stem cell niche micro-environment as therapeutic strategies in aging. Front Cell Dev Biol 11: 1162136, 2023.
163. Fathi E, Farahzadi R, Sheervalilou R, Sanaat Z and Vietor I: A general view of $CD33^+$ leukemic stem cells and CAR-T cells as interesting targets in acute myeloblatsic leukemia therapy. Blood Res 55: 10-16, 2020.
164. Fathi E, Valipour B, Vietor I and Farahzadi R: An overview of the myocardial regeneration potential of cardiac $c\text{-}Kit^+$ progenitor cells via PI3K and MAPK signaling pathways. Future Cardiol 16: 199-209, 2020.